In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: June 7, 2023

RICHARD VAN DYCKE,	*	PUBLISHED
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Petitioner,	*	No. 18-106V
	*	
v.	*	Special Master Nora Beth Dorsey
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Tetanus-Diphtheria-Acellular Pertussis ("Tdap") Vaccine; Polymyalgia Rheumatic ("PMR"); Temporal Arteritis; Giant Cell Arteritis ("GCA").
	*	
Respondent.	*	
	*	

Edward Kraus, Kraus Law Group, LLC, for Petitioner.
Emilie Williams, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION[1]

I. INTRODUCTION

On January 23, 2018, Richard Van Dycke ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2018).[2] Petitioner alleges that he suffered polymyalgia rheumatic ("PMR") and temporal arteritis, also known as giant cell arteritis ("GCA"), as the result of a

[1] Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2018) ("Vaccine Act" or "the Act"). All citations in this Decision to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

tetanus-diphtheria-acellular pertussis ("Tdap") vaccination administered on August 4, 2016. Petition at Preamble (ECF No. 1). Respondent argued against compensation, stating that "this case [was] not appropriate for compensation under the [Vaccine] Act." Respondent's Report ("Resp. Rept.") at 1-2 (ECF No. 51).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioner has failed to provide preponderant evidence that his Tdap vaccine caused his GCA and/or PMR and thus has not satisfied his burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, the petition must be dismissed.

II. ISSUES TO BE DECIDED

Diagnosis is not at issue. Joint Prehearing Submission, filed Aug. 23, 2022 at 1 (ECF No. 73). The parties stipulated that Petitioner received a Tdap vaccine on August 4, 2016, and 19 days later experienced an "abrupt onset of symptoms" that marked the onset of his GCA/PMR. Id.

The central issue is whether Petitioner has provided preponderant evidence of causation for all three Althen prongs. Petitioner asserts that he has met his burden under the Althen prongs. Petitioner's Prehearing Memorandum ("Pet. Memo."), filed Aug. 2, 2022, at 8-17 (ECF No. 71). Respondent disagrees and argues that Petitioner failed to submit preponderant evidence that his Tdap vaccine more likely than not caused his GCA/PMR. Resp. Prehearing Brief ("Resp. Br."), filed Aug. 23, 2022, at 15-20 (ECF No. 74).

III. BACKGROUND

A. Medical Terminology

GCA is a "systemic vasculitis[3] with two disease components: vessel wall inflammation inducing arterial stenosis/occlusion and a systemic inflammation leading to polymyalgias . . . and malaise." Pet. Exhibit ("Ex.") 64 at 2.[4] The first component is a "large-vessel vasculitis" that involves the "aorta and external carotid arteries and their branches," with abnormalities of the inner layers of the blood vessels and obstruction, "leading to ischemic manifestations such as temporal headaches, jaw claudication, scalp tenderness[,] and temporal artery involvement." Pet.

[3] Vasculitis is the "inflammation of a blood or lymph vessel." Vasculitis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=52617 (last visited Apr. 7, 2023).

[4] Jiusheng Deng et al., TH17 and TH1 T-Cell Responses in Giant Cell Arteritis, 121 Circulation 906 (2010).

Ex. 50 at 1.[5] Other characteristics of GCA include "proliferative inflammation, often with giant cells and granulomas;[6] headache; pain with chewing;" signs of "systematic inflammation" including weight loss, fatigue, and fever; as well as increased erythrocyte sedimentation rate ("ESR") and C-reactive protein ("CRP") levels. Giant Cell Arteritis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition? id=58337 (last visited Apr. 3, 2023); see Pet. Ex. 50 at 2; Pet. Ex. 53 at 1.[7] Vision loss may also occur. Pet. Ex. 50 at 2. GCA "occurs exclusively" in individuals over 50 years but is more prevalent among those over 70 years. Id.

"No specific biological marker of GCA has been identified, and the diagnosis is usually established by temporal artery biopsy." Pet. Ex. 50 at 2. Corticosteroids are the main form of treatment for GCA and a response to corticosteroids is one validation of diagnosis. Id.; see also Pet. Ex. 28 at 2.[8]

The second component of the disease is PMR, "an inflammatory condition of unknown cause characterized by aching and morning stiffness in the cervical region and shoulder and pelvic girdles. It usually responds to . . . corticosteroids and has a favorable prognosis." Pet. Ex. 11 at 1.[9] "Systemic manifestations (fever, malaise, fatigue, [] and weight loss) occur . . . in 30-60% of the patients." Pet. Ex. 12 at 3.[10] It may occur together with GCA. Id. "Arthroscopic, radioisotopic, and magnetic resonance imaging (MRI) studies of patients with [PMR] all have indicated the presence of a synovitis in proximal joints and periarticular structures." Pet. Ex. 11 at 3. "The synovitis . . . is histologically mild and is characterized by a predominance of macrophages and T cells, mostly CD4+ helper T cells. These features are very similar to those of the vascular lesions of [GCA]." Id.

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[5] Kim-Heang Ly et al., Pathogenesis of Giant Cell Arteritis: More Than Just an Inflammatory Condition?, 9 Autoimmunity Rev. 635 (2010).

[6] A granuloma refers to an "aggregation of mononuclear inflammatory cells or a similar collection of epithelioid cells; it is usually surrounded by a rim of lymphocytes and often includes multinucleated giant cells. . . . Granuloma formation represents a chronic inflammatory response that can be initiated by infectious or noninfectious agents." Granuloma, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=20934 (last visited Apr. 7, 2023).

[7] Wei Ma Krupa et al., Trapping of Misdirected Dendritic Cells in the Granulomatous Lesions of Giant Cell Arteritis, 161 Am. J. Pathology 1815 (2002).

[8] L. Smeeth et al., Incidence of Diagnosed Polymyalgia Rheumatica and Temporal Arteritis in the United Kingdom, 1990-2002, 65 Annals Rheumatic Diseases 1093 (2006).

[9] Carlo Salvarani et al., Polymyalgia Rheumatica and Giant-Cell Arteritis, 347 New Eng. J. Med. 261 (2002).

[10] Gideon Nesher & Gabriel S. Breuer, Giant Cell Arteritis and Polymyalgia Rheumatica: 2016 Update, 7 Rambam Maimonides Med. J. e0035 (2016).

The diagnosis of PMR is made clinically as there is no diagnostic test specific for the illness. Pet. Ex. 12 at 5. Clinical criteria include morning stiffness lasting more than 45 minutes, hip pain or decreased range of motion, and shoulder bursitis and hip synovitis or bursitis.[11] Id. at 6 tbl.3. PMR is "thought to have a benign course, with a variable degree of treatment-related morbidity." Id. at 6. "It is unknown whether PMR is just an expression of an underlying GCA. More likely, it seems that both are a result of unknown causative factor (or factors), sometimes expressed as PMR, sometimes as GCA, and sometimes as a combination." Id. at 7.

B. Procedural History

Petitioner filed his petition on January 23, 2018, alleging that the Tdap vaccine he received on August 4, 2016, was the cause in fact of his GCA and PMR. Petition at Preamble. On September 28, 2018, Respondent filed an initial Rule 4(c) Report offering a preliminary summary of the filed medical records but indicated that medical personnel at the Division of Injury Compensation Programs ("DICP") had not yet been able to review the claim and offer an opinion as to Respondent's position. Resp. Rept. (ECF No. 13).

Pursuant to the Court's Order, Petitioner filed an expert report by Dr. M. Eric Gershwin on March 12, 2018. Pet. Ex. 23. Respondent filed an expert report by Dr. Erin Wilfong on May 31, 2019. Resp. Ex. B. And on July 16, 2019, Petitioner filed a supplemental expert report by Dr. Gershwin. Pet. Ex. 103. Chief Special Master Corcoran issued a briefing schedule. Non-PDF Order dated July 29, 2019. The matter was subsequently reassigned to the undersigned on October 4, 2019. Notice of Reassignment dated Oct. 4, 2019 (ECF No. 31).

Petitioner filed a second supplemental expert report by Dr. Gershwin on October 8, 2019, and simultaneously requested a status conference asking the undersigned to vacate the current briefing schedule. Pet. Ex. 108; Pet. Motion, filed Oct. 8, 2019 (ECF No. 36). The undersigned held a status conference on October 17, 2019. Order dated Oct. 17, 2019 (ECF No. 37). The undersigned vacated all pending deadlines of the previously set briefing schedule and ordered Respondent to file a supplemental expert report. Id. On December 20, 2019, Respondent filed a supplemental expert report by Dr. Wilfong. Resp. Ex. C. On May 6, 2020, Respondent filed his Rule 4(c) Report stating his position that Petitioner was not entitled to compensation, particularly because "[P]etitioner ha[d] failed to meet his burden of demonstrating by preponderant evidence a scientifically reliable theory of vaccine causation." Resp. Rept. at 7 (ECF No. 51).

A Rule 5 status conference was held on May 19, 2020, where the undersigned provided her preliminarily findings, and encouraged the parties to resolve the matter informally. Rule 5 Order dated May 20, 2020, at 2 (ECF No. 52).

The parties entertained settlement discussions from May to August 2020. See ECF Nos. 53-55. Thereafter, Respondent filed a status report maintaining his position that compensation was unwarranted and requested to proceed on a litigation track. Resp. Status Rept., filed Aug. 19, 2020 (ECF No. 56). At a status conference on September 2, 2020, the undersigned explained

[11] For the PMR classification criteria, see Pet. Ex. 12 at 6 tbl.3.

that she likely would not be able to resolve this case on a ruling on the record and would need a hearing. Order dated Sept. 2, 2020 (ECF No. 57). The parties agreed that a hearing was necessary, and a pre-hearing order was issued. Id.; Pre-Hearing Order dated Oct. 5, 2020 (ECF No. 59).

Petitioner filed his pre-hearing brief on August 2, 2022, and Respondent filed his pre-hearing brief on August 23, 2022. Pet. Memo.; Resp. Brief. An entitlement hearing was held on September 27, 2022 via Webex videoconference. Transcript ("Tr.") 1. Dr. Gershwin and Dr. Wilfong testified. Tr. 3. The parties did not wish to file post-hearing briefs. Pet. Status Rept., filed Oct. 26, 2022 (ECF No. 97).

This matter is now ripe for adjudication.

C. Factual History

1. Medical History

Prior to August 2016, Petitioner's medical history consisted of gastroesophageal reflux disease, benign vertigo, shingles, and rotator cuff and bicep tendon injuries. Pet. Ex. 2 at 7. Petitioner was 62 years old and in his "usual state of health" when he received the Tdap Boostrix vaccination on August 4, 2016. Pet. Ex. 5 at 2; Joint Prehearing Submission at 1.

On August 24, 2016, Petitioner saw chiropractor Dr. Ralph Destephano with complaints of moderate low back pain. Pet. Ex. 8 at 5. Petitioner reported restricted movement and a "numb ache type and throbbing pain" in his sacroiliac (hip and pelvic) area and lower lumbar area. Id. He also complained of right shoulder pain. Id. Overall, Petitioner stated it was usually worse in the morning and aggravated by movements. Id. Petitioner relayed that "he had a tetanus vaccination a couple of weeks ago which he believe[d] [was] the reason for his symptomatology." Id. Assessment was "acute exacerbation of a chronic condition." Id. at 6.

On September 14, 2016, Petitioner presented to Dr. Andreea Maria Costea (resident) and Dr. Monica J. Fudala (physician) for "diffuse, bilateral joint pain in shoulders, hands, hips[,] and knees that started [three] weeks ago." Pet. Ex. 3 at 7, 10. Petitioner also presented with concern of "fluid" in his right ear since that morning. Id. at 7-8. Presentation notes included that Petitioner "got Tdap [vaccine] on [August 4, 2016] started to have muscle aches from then." Id. at 7. Dr. Costea added that Petitioner "received a Tdap booster and had gone on a long bike ride. He attributed the pain to [the bike ride] at first, but it ha[d] persisted. He report[ed] the pain in joints [was] worse in the morning or after long periods of rest and [got] better with movement." Id. at 8. Dr. Fudala noted Petitioner also had jaw pain and "stiffness in hands." Id. at 10. Petitioner reported chills and a low-grade temperature but no fever. Id. at 8, 10. He denied cough and runny nose. Id. at 8. Petitioner also reported taking ibuprofen "and it ha[d] helped, but [symptoms] [had not] resolved." Id. Lab tests done that day revealed elevated ESR and CRP levels, and positive anti-nuclear antibody ("ANA") titer. Id. at 38-41. The assessment was "[j]oint pain bilaterally in hands, knees[,] and hips possible [rheumatoid arthritis]." Id. at 10, 37. He was referred to physical therapy and to a rheumatologist. See id.

At his initial physical therapy evaluation on September 19, 2016, Petitioner reported right shoulder pain "worsening after booster shot." Pet. Ex. 8 at 10. He had pain in his knees and shoulders getting out of bed and aching in his joints when they were cold. Id. He also reported difficulty sleeping and difficulty reaching in front of him. Id. "[R]eaction to booster shot" was documented. Id.

Petitioner presented to rheumatologist Dr. Kathryn Kiehn on September 30, 2016 for joint pain, weight loss, chills, and swollen hands. Pet. Ex. 1 at 10. History notes indicated Petitioner received the Tdap vaccine on August 4, 2016 and had no issues until two weeks after when he had "acute onset of polyarticular joint pains." Id. He had stiffness in his jaw and neck, hand and feet pain with swelling, and right elbow and shoulder pain. Id. He denied back pain and muscle pain. Id. Petitioner reported if he was active, then he was "not as bothered by it," but if he sat, then he had "trouble getting up." Id. Similarly, Petitioner reported morning stiffness for about two-and-one-half hours per day. Id. On examination, he had mild tenderness to palpitation ("TTP") of all proximal interphalangeal ("PIP") joints with trace swelling, TTP of bilateral wrists, TTP of the right elbow, and pain with external rotation of the right shoulder. Id. at 11. Dr. Kiehn noted Petitioner's prior lab results showing an elevated ESR (56 mm/hour; normal range 0-20) and CRP (5.3 mg/dL; normal range 0.0-0.5) and negative rheumatoid factor ("RF"). Id. Dr. Kiehn's assessment was inflammatory arthritis, "new onset in August 2016 [two] weeks after had Tdap, suspect related to this (reactive) but could also just be onset of new inflammatory arthritis." Id. at 10. She explained to Petitioner the difference between the two suspected causes and stated that "time [would] help differentiate." Id. Petitioner was prescribed a Medrol Dose Pak, followed by naproxen. Id.

On October 8, 2016, Petitioner saw his regular chiropractor Dr. Lawrence Needham.[12] Pet. Ex. 22 at 21. Petitioner's complaints that day were for "frequent moderate diffuse right [shin] symptoms of a burning nature" and "moderate diffuse right posterior upper arm symptoms of a generally achy but occasionally sharp nature" that began one month ago. Id. Petitioner reported these symptoms began following his Tdap vaccine on August 4, 2016. Id. Dr. Needham assessed Petitioner with right calf atrophy, shin splints, rotator cuff syndrome, and myalgia and myositis. Id. Various spinal adjustments and upper and lower extremity manipulations were performed, along with application of moist heat, continuous ultrasound, and trigger point therapy. Id.

Petitioner's symptoms improved with the steroids; however, on Friday, October 7, 2016, the day after finishing the Medrol Dose Pak, his joint and muscle pains returned, and he began experiencing double vision. Pet. Ex. 3 at 114. He called Dr. Kiehn two days later (Sunday, October 9, 2016) who advised him to go to the emergency department ("ED"). Id.

Accordingly, on October 9, 2016, Petitioner presented to the ED complaining that his left eye had been "not right" since Friday (October 7, 2016) and of a "stiff neck." Pet. Ex. 3 at 49. He reported his vision would "be double or just blurred when [he] turn[ed] [his] head to [the] right and look[ed] out left eye." Id. The ED notes indicated Petitioner "had Tdap in August and had reaction to it with muscle weakness and multi[ple] workups since[,] symptoms improv[ed]

[12] Medical records indicate Petitioner had seen Dr. Needham since at least 2013. See Pet. Ex. 22.

with steroids." Id. Petitioner was "taking [naproxen] for painful joints since receiving Tdap, also completed steroids for same complaint." Id. at 50. Additionally, notes included "weeks of fatigue, muscle weakness[,] and loss of weight. . . . [T]hought to have [reaction] to Tdap." Id. at 58. The Tdap Boostrix was recorded as an allergy. Id. at 50. The impression was "left 6th nerve palsy"[13] and ophthalmoplegia.[14] Id. at 58, 157. Petitioner was admitted to the hospital that day. Id. at 58. A neurology consultation, blood work, and imaging studies were also ordered. Id. That night, Petitioner received a dose of prednisone and ketorolac. Id. at 114.

Dr. Ramsey Michael Wehbe assumed the care of Petitioner on October 10, 2016. Pet. Ex. 3 at 157. On that day, Petitioner was "[n]ot complaining of any muscle/joint pain or stiffness" but "[s]till [had] double vision with left gaze." Id. Dr. Wehbe's notes stated Petitioner's "[s]ymptoms began shortly after getting Tdap. Also cut his finger on a saw [four] days after Tdap. Began to experience shoulder girdle and hip tightness with riding bike. This evolved into pain/inflammation of hands/feet and knees with swelling of his hands and feet." Id. Petitioner also reportedly had "weight loss and 'muscle atrophy'" as well as significant fatigue. Id. Petitioner's "[s]tiffness/pain dramatically improved with empiric steroids, diplopia occurred immediately after cessation." Id. at 161. On physical examination, Dr. Wehbe documented "[left] [cranial nerve] VI palsy. Significant nystagmus[15] with [right] gaze, disconjugate gaze with [left] gaze . . . . CNS otherwise intact." Id. at 158. Regarding etiology, Dr. Wehbe wrote "[p]resentation [was] highly suspicious for vasculitis process, particularly GCA in the setting of underlying PMR. Other rheumatologic process possible, low suspicion for infectious process." Id. at 161.

Also on October 10, 2016, Petitioner saw consulting neurologist Dr. Ian Katznelson. Pet. Ex. 3 at 114. The history noted that "in early August [Petitioner] had a pertussis vaccine. He did fine, but [three] weeks later started to develop very diffuse joint aches with pain involving the

[13] Sixth nerve palsy is the "paralysis of the lateral rectus muscle of the eye due to lesion of the abducens nerve, with internal strabismus and diplopia." Abducens Palsy, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=95777 (last visited Apr. 3, 2023).

[14] Ophthalmoplegia is the "paralysis of the eye muscles." Ophthalmoplegia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=35269 (last visited May 16, 2023).

[15] Nystagmus is "an involuntary, rapid, rhythmic movement of the eyeball, which may be horizontal, vertical, rotatory, or mixed, i.e., of two varieties." Nystagmus, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=34565 (last visited Apr. 3, 2023).

[temporomandibular joints ("TMJs")],[16] shoulders, hips, [and] knees." Id. Dr. Katznelson noted Petitioner was on a six-day course of prednisone and was "preparing to take some high doses of naproxen," but that on Friday, Petitioner developed "the sudden onset of diplopia[17] looking left horizontally." Id. "No eye pain, no true jaw claudication, tongue pain[,] or headache with any of this" was noted. Id. at 115. Additionally, Petitioner reportedly "had chills at home, but no true fever." Id. "Allergy: is listed now to the pertussis vaccine" was recorded. Id. Dr. Katznelson reviewed Petitioner's labs and imaging studies done that day including an elevated ESR (66 mm/hour) and CRP (13.7 mg/dL). Id. at 115, 233, 240.

Dr. Katznelson determined Petitioner had "a systemic inflammatory process now involving the cranial nerves. The differential diagnosis could include vasculitis; less likely an infection, although this [was] certainly possible. [He] [] imagine[d] some sort of hypersensitivity reaction after the pertussis vaccine [was] also possible." Pet. Ex. 3 at 116. "Another issue would be that of perhaps a temporal artery biopsy, although this would be a little bit unusual for [GCA]. He ha[d] no headache and ha[d] a 6th nerve paresis." Id. Dr. Katznelson ordered additional studies. Id.

Petitioner underwent a left temporal artery biopsy on October 11, 2016, which revealed features consistent with vasculitis, including temporal arteritis." Pet. Ex. 3 at 216, 319. And on October 12, 2016, Petitioner underwent a lumbar puncture revealing an elevated white blood cell count.[18] Id. at 228-29, 327.

On October 13, 2016, Petitioner was evaluated by Dr. Yien Li for "worsening myalgias, weakness." Pet. Ex. 3 at 172-73. At that time, Petitioner was on intravenous ("IV") steroids. Id. at 173. Dr. Li determined the MRI and biopsy studies were "suggestive of large vessel vasculitis" and the lumbar puncture "showed mild lymphocytosis." Id. Thus the "running thought" was that "this [was] temporal arteritis however what [did not] fit [was] how [Petitioner] ha[d] CN6 palsy which could be consistent with small vessel vasculitis." Id. Given the eye complaint and cerebrospinal fluid ("CSF") lymphocytosis, Dr. Li questioned whether it could be syphilis "as it can masquerade and cause both large vessel and small vessel vasculitis." Id. The syphilitic screening came back negative. Id. at 178.

Petitioner was discharged from the hospital on October 14, 2016. Pet. Ex. 3 at 120-23. His discharge diagnoses were "double vision, joint pain, [and] temporal arteritis/vasculitis." Id.

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[16] The temporomandibular joint is "a bicondylar synovial joint formed by the head of the mandible and the mandibular fossa, and the articular tubercle of the temporal bone." Articulatio Temporomandibularis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=59108 (last visited Apr. 3, 2023).

[17] Diplopia is "the perception of two images of a single object." Diplopia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=14354 (last visited Apr. 3, 2023).

[18] Two samples of cerebrospinal fluid ("CSF") were analyzed on the same day, at the same time, revealing elevated white blood cell counts of 9 and 6 (normal range 0-5). Pet. Ex. 3 at 28.

at 120. The summary of his hospital course included that he was a "previously healthy male with no known medical issues," who had a "subacute presentation of shoulder/hip stiffness with associated swelling and pain of hands, knees, and feet responsive to empiric steroid therapy, with subsequent acute onset diplopia." Id. at 122. He was scheduled to have his last steroid infusion the following day and was prescribed prednisone for the next month. Id. at 122-23. Petitioner was instructed to follow up with rheumatology, ophthalmology, and neurology. Id. The same day as his discharge, Petitioner saw Dr. Michael Blair for an evaluation of "left eye diplopia on left sided gaze" with history of temporal arteritis and sixth nerve palsy. Pet. Ex. 6 at 1. Examination revealed limited abduction on the left eye and poor light response. Id. Petitioner was referred to a strabismologist. Id. at 2.

On October 21, 2016, Petitioner presented to ophthalmologist Dr. Lisa Thompson for temporal arteritis involving the left eye "associated with diplopia, strabismus."[19] Pet. Ex. 7 at 3. History indicated Petitioner's symptoms were of moderate severity and had been present for two weeks. Id. Dr. Thompson diagnosed Petitioner with a sixth cranial nerve palsy and counseled that it "may improve without treatment if it [was] due to blockage of a small blood vessel to the nerve" and that it would "usually improve and resolve within three months," but that "any underlying systematic disease [would] need to be treated." Id. at 4.

Petitioner followed up with Dr. Katznelson on October 24, 2016. Pet. Ex 3 at 18-19. Petitioner reported the "diplopia [was] improving, but not totally resolved," and he "noticed that his right ear seemed 'full' around [discharge] time from the hospital but no discrete hearing loss." Id. at 18. Petitioner's joint/body aches were gone but he was still on prednisone daily. Id. Dr. Katznelson recorded that Dr. Ben Dov looked in Petitioner's ears and "canals were clear." Id. On examination, Petitioner had nystagmus, which Dr. Katznelson believed he "[d]id not clearly see" in the hospital. Id. at 19. Dr. Katznelson questioned whether Petitioner's "ear fullness [could] be related, i.e, vascular [cranial nerve] VII involvement." Id. He recommended a computerized tomography ("CT") angiogram of the head and neck to evaluate the vessels and a repeat brain MRI. Id.

On October 28, 2016, Petitioner returned to Dr. Kiehn for his one-month GCA follow-up appointment. Pet. Ex. 1 at 7-8. No changes were reported. Id. At a follow-up visit on November 23, 2016, Dr. Thompson noted that Petitioner's left isolated sixth nerve palsy had improved since his last visit. Pet. Ex 7 at 6-7.

Dr. Dov saw Petitioner on November 28, 2016 following his hospitalization. Pet. Ex. 3 at 29-32. Dr. Dov recorded that Petitioner's temporal arteritis and vasculitis was confirmed on biopsy and that while he was on steroids, his symptoms improved. Id. at 31-32. Dr. Dov reassured Petitioner that his steroid-induced hyperglycemia would resolve. Id. at 32.

On November 30, 2016, Petitioner had a follow-up appointment with Dr. Kiehn. Pet. Ex. 1 at 4-5. Petitioner reported he had been feeling better, his double vision was improving, and felt

[19] Strabismus is "an eye condition in which the visual axes cannot be directed at the same point of fixation under normal conditions of seeing." Strabismus, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=47369 (last visited Apr. 3, 2023).

"50% improvement." Id. at 4. On examination, his nystagmus had also improved. Id. Petitioner reported he planned to return to work the following day. Id. at 5.

On December 5, 2016, Petitioner saw Dr. Katznelson for a follow-up appointment. Pet. Ex. 3 at 33. Dr. Katznelson noted Petitioner had no recurrent muscle aches and his double vision was improving. Id. There was "no jaw claudication, no headache, and his ear fullness [] resolved." Id. However, Petitioner still noticed "horizontal diplopia in the extremes of left gaze." Id. But Dr. Katznelson noted objective measurements from the ophthalmologist suggested he was improving. Id. No nystagmus were observed on examination. Id. at 34. The CT angiogram of the head was negative and the brain MRI did not show any acute findings. Id. at 33. Dr. Katznelson's diagnosis was GCA "which appear[ed] to be improving;" however, he did not know why Petitioner had nystagmus "for a brief period of time" and it was "not totally clear why [Petitioner] had elevated white cells in the spinal fluid." Id. at 34. Dr. Katznelson expressed concern for intracranial vasculitis. Id.

From January 2017 to March 2017, Petitioner had follow-up visits with rheumatologist Dr. Kiehn, ophthalmologist Dr. Thompson, and neurologist Dr. Katznelson. Throughout this time, he reported overall improvement in his vision. See Pet. Ex. 1 at 1; Pet. Ex. 7 at 1; Pet. Ex. 3 at 35; Pet. Ex. 19 at 16.

Petitioner returned to Dr. Katznelson on May 23, 2017. Pet. Ex. 16 at 10. Petitioner reported that approximately two weeks prior, he was "yanking on a very taut wire" at work and about three days later, developed "an achy central, non-radiating posterior neck pain that [] persisted." Id. He did not report joint pain or diffuse body pains "as before." Id. "Neck rotation somewhat worsen[ed] the symptoms." Id. Dr. Katznelson documented that "[w]hile neck pain could be cervical spine," given Petitioner's history, he told Petitioner "to be vigilant for re-development" of GCA and PMR. Id. at 11. Petitioner requested that his ESR and CRP levels be checked before making further treatment decisions. Id. Lab tests done that day showed normal ESR (3 mm/hour) and normal CRP (<0.5 mg/dL) levels. Id. at 16-17. Petitioner saw Dr. Kiehn on May 30, 2017 and reported that his neck pain had resolved. Pet. Ex. 19 at 13.

At a rheumatology follow-up on October 2, 2017, Petitioner had normal inflammatory markers (ESR and CRP) and was doing well. Pet. Ex. 9 at 3. He was continuing to take a lower dose of prednisone. Id. Petitioner reported he had "slightly more fatigue" (not activity-limiting), but it was "[n]ot as severe when he had active GCA (he would fall asleep on his way home)." Id. He was maintaining a regular exercise regimen and had an active job. Id. He was instructed to follow up with Dr. Kiehn in three months. Id.

By December 1, 2017, Petitioner had been off prednisone for six weeks and had been doing well until four days prior, when he started to have pain and swelling in his feet, ankles, knees, hands, and wrists. Pet. Ex. 19 at 7-8. Dr. Kiehn assessed Petitioner with inflammatory arthritis and GCA. Id. at 8. He was prescribed another course of prednisone and instructed to follow up. Id.

From January 2018 to March 2018, Petitioner had follow-up appointments with Dr. Kiehn. Pet. Ex. 19 at 1-8. His symptoms continued to improve and by March he was no longer taking prednisone. Id. at 1. The plan again was to follow up in three months. Id.

On July 10, 2018, Petitioner presented to Dr. Kiehn for a six-month follow-up appointment for his GCA. Pet. Ex. 121 at 4. At that time, he was not taking prednisone. Id. Petitioner denied joint pain, headaches, new vision changes, and jaw pains. Id. "Double vision overall [was] stable, ha[d] one area when look[ed] to left where [he] [saw] double vision." Id. Petitioner's ophthalmologist reportedly told him the area of double vision was "unlikely to go away." Id. Labs done that day were unremarkable. Id. at 8-11. Dr. Kiehn's assessment was GCA, inflammatory arthritis, long term use of systemic steroids, and weight loss. Id. at 4. She noted that Petitioner was currently "doing well." Id.

Approximately one year later, on Friday, August 2, 2019, Petitioner presented to Dr. Katznelson for a PMR follow-up. Pet. Ex. 122 at 25. Dr. Katznelson noted that he had not seen Petitioner "in over [two] years" and that Petitioner had "been off prednisone since early 2018 and had been symptom-free." Id. Petitioner reported that "[three] weeks ago he started to develop a tingling on the left temple but only with his head lying on the right side, mild bilateral retro-orbital pain, as well as [] pain in both jaws when opening his mouth wide. Sometime last week he had more of a headache." Id. He reportedly contacted Dr. Kiehn who "placed him empirically on prednisone" for one day on Tuesday that week. Id. After taking it, "his symptoms completely disappeared and [] had no recurrence." Id. Dr. Katznelson recorded that Petitioner's ESR and CRP levels were checked prior to taking prednisone on Tuesday and they were normal. Id. He did not have "diplopia, vision loss, dysphagia, vertigo, neck pain[,] focal weakness or sensory loss. No other focal neurological symptoms." Id. On examination Petitioner had a "hint of right [eye] ptosis"[20] which Petitioner attributed to contact irritation. Id. at 28. Dr. Katznelson documented that he "[s]poke at length with Dr. Kiehn" about Petitioner's case who suggested that "given the normal inflammatory markers after three weeks of symptoms and disappearance of symptoms after single dose of [p]rednisone without redevelopment it was less likely that the symptoms were related to [GCA]." Id. Dr. Katznelson ordered an MRI of the brain and a magnetic resonance angiography ("MRA") of the head and neck. Id. Petitioner was instructed to take prednisone if his symptoms redeveloped. Id.

On August 23, 2019, Petitioner followed up with Dr. Katznelson. Pet. Ex. 122 at 6. History indicated he was doing better since the last visit. Id. The only concern was "[o]nce or twice a week [Petitioner] [got] very brief tingling feeling in the left temple when he put[] his left temple on a pillow, but no pain." Id. He also "[s]till ha[d] some pain near the TMJs but only when he open[ed] his jaw." Id. Dr. Katznelson reviewed the MRI and MRA which were negative for acute changes. Id. His physical examination was unremarkable except for pain with the jaw opening. Id. at 8. Dr. Katznelson noted that he "[could not] explain [Petitioner's] left temple tingling but it [was] not typical for GCA." Id. Additionally, since Petitioner "continue[d] to have the jaw issue," repeat labs of his ESR and CRP levels were ordered "to assure they [were] not uptrending in any way." Id. at 9. Dr. Katznelson noted that if the ESR and CRP

[20] Ptosis is the "drooping of the upper eyelid." Ptosis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=42014 (last visited Apr. 4, 2023).

levels were not uptrending, then it was "highly unlikely that this would be GCA, and perhaps just more of a typical TMJ syndrome." Id. The plan was for Petitioner to return in three months and take prednisone if needed. Id.

No other relevant medical records were submitted.

2. Petitioner's Affidavit

Petitioner executed an affidavit on December 21, 2017. Pet. Ex. 10 at 3. Prior to August 2016, Petitioner indicated he was in good health. Id. at ¶ 2. He explained he got the Tdap vaccine on August 4, 2016 because he was expecting a grandchild and "did not want to expose the baby to potential illness." Id. at ¶¶ 3-4. The week following vaccination, Petitioner experienced an elevated temperature (99°F), tiredness, and "was not [his] normal self." Id. at ¶ 5.

Three weeks after receiving the Tdap vaccine, Petitioner went on a "long bike ride" and two days later, on August 23, 2016, Petitioner reported he "woke up in pain." Pet. Ex. 10 at ¶ 6. He initially attributed the pain to soreness from his bike ride and expected it to resolve on its own. Id. Instead, "the pain worsened." Id. at ¶ 7. He "realized that this was not muscle pain from a workout, but a very profuse joint pain. All of [his] joints were affected, even [his] jaw." Id. Soon after experiencing the "acute joint symptoms on August 23, 2016," Petitioner called his primary care provider, but the first available appointment was not until September. Id. at ¶ 8.

Petitioner was able to get an appointment with his primary care doctor on September 14, 2016. Pet. Ex. 10 at ¶¶ 8-9. He explained he had blood work done that showed "elevated inflammatory markers" and he was referred to a rheumatologist. Id. at ¶ 9. The rheumatologist prescribed steroids and Petitioner "began feeling better while taking the steroids." Id. at ¶¶ 10-11. He recalled his "joint pain and body aches diminished significantly" during this time. Id. at ¶ 11. However, the day after finishing the steroid prescription, Petitioner's "joint pain and body aches returned" and he began "having double vision." Id. at ¶ 12. After calling his rheumatologist about his symptoms, he was advised to "seek emergency care immediately." Id. at ¶ 13.

He was subsequently admitted to the hospital on October 9, 2016, and remained there until October 14. Pet. Ex. 10 at ¶ 14. Petitioner averred he was diagnosed with "[PMR] with temporal arteritis or GCA" and that his rheumatologist told him "it was not uncommon for people suffering from [PMR] to develop GCA." Id. at ¶ 15.

Petitioner stated he remained on steroids for over one year. Pet. Ex. 10 at ¶ 16. While on them, he explained his "body aches and joint pain significantly improved" and his "double vision improved somewhat, but [] continued to have trouble with [his] left eye." Id. When he weaned off the steroids in mid-October 2017, he "experienced some increased fatigue, but [his] joint pain remained stable and tolerable until late November when the pain flared up again." Id. at ¶ 17. He was prescribed steroids again because he was told "the inflammation had returned." Id. at ¶ 18. Additionally, Petitioner claimed the "double vision in his left eye has persisted." Id. at ¶ 19.

D. Expert Reports

1. Petitioner's Expert, Dr. M. Eric Gershwin[21]

a. Background and Qualifications

Dr. Gershwin is board certified in internal medicine, rheumatology, and allergy and clinical immunology. Pet. Ex. 136 at 2. He completed his M.D. at Stanford University. Id. He currently works in the Division of Rheumatology, Allergy, and Clinical Immunology at the University of California Davis School of Medicine as director of the Allergy-Clinical Immunology Program and as a Distinguished Professor.[22] Id. at 1; Tr. 7-8. In this position, he still sees patients. Tr. 8-9. He estimated he has treated "several hundred" patients with GCA or PMR over his career and has written and researched on GCA or PMR. Tr. 9, 13. Dr. Gershwin has held various editor and reviewer positions on medical journals, and has authored or co-authored over 1,000 publications during his career. Pet. Ex. 136 at 4-139.

b. Opinion

Dr. Gershwin opined, more likely than not, that Petitioner's Tdap vaccine caused him to develop GCA and PMR through the activation of the immune system leading to an inflammatory response. Pet. Ex. 23 at 4-7; Pet. Ex. 108 at 1; Tr. 15, 23, 26.

i. Althen Prong One

Dr. Gershwin first explained the pathogenesis of GCA. Tr. 23. He described GCA as "a process by which vasculitis occurs because there's some mechanism that pulls or attracts activated immune cells into the vessel[,] producing inflammation and then inflammation produces swelling[,] ischemia, [and] oxygen deprivation and therefore potential for cranial nerve dysfunction, headaches[,] and so forth." Tr. 24. He conceded that the specific etiology of GCA is unknown, but asserted that vaccination, which activates the immune system, can start the process. Tr. 39.

At times, Dr. Gershwin referred to GCA/PMR as an "autoimmune disease," and he stated that as with every autoimmune condition, there is a genetic component, and probably multiple genes which are associated with the illness, which make individuals more susceptible. Tr. 40.

[21] Dr. Gershwin submitted three expert reports in this matter and testified at the hearing on September 27, 2022. Pet. Exs. 23, 103, 108; Tr. 5, 120.

[22] At the time Dr. Gershwin authored his expert reports, he was also chief of this division. Pet. Ex. 24 at 1.

For example, an association has been suggested between the human leukocyte antigen ("HLA")[23] haplotype,[24] HLA-DRB1 *04, and GCA. Pet. Ex. 23 at 3 (citing Pet. Ex. 50 at 5); see also Pet. Ex. 112 at 3 (stating studies have shown an association of GCA and PMR with alleles at HLA-DRB1);[25] Pet. Ex. 38 at 8 (discussing genetic markers in GCA/PMR).[26]

Additionally, Dr. Gershwin discussed immunosenescence,[27] defined as the immune system dysregulating with age. Pet. Ex. 23 at 8; Tr. 25, 51 (citing Pet. Ex. 130 at 12 (describing that the balance of inflammatory and anti-inflammatory immune responses can become disturbed in the elderly due to the aging of both the innate and adaptive immune systems));[28] see also Pet. Ex. 110 at 1 (discussing that age has an influence on humoral immune responses to vaccination).[29] In addition, he described the "aging of vessels," and the senescence of dendritic endothelial cells. Tr. 25, 50, 53. Dr. Gershwin therefore explained that individuals older than 50 years of age are more susceptible to GCA "from both the concept of immune dysregulation" and "the target tissue itself, the endothelial cells within the vessels." Tr. 25; see also Tr. 36; Pet. Ex

[23] Human leukocyte antigens are "histocompatibility antigens governed by genes of the HLA complex (the human major histocompatibility complex), a region on the short arm of chromosome 6 containing several genetic loci, each having multiple alleles. . . . The A, B, C, and DR antigens are defined and typed by serologic reactions. The D antigens are defined and typed by one-way mixed lymphocyte culture (MLC) using panels of HLA-D-homozygous typing cells." Human Leukocyte Antigens, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=56923 (last visited May 24, 2023).

[24] Haplotype is "a set of alleles of a group of closely linked related genes on one chromosome of an individual, usually inherited as a unit; used particularly of the combination of alleles of the HLA complex." Haplotype, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=21430 (last visited May 24, 2023).

[25] A. Soriano et al., Giant Cell Arteritis and Polymyalgia Rheumatica After Influenza Vaccination: Report of 10 Cases and Review of the Literature, 21 Lupus 153 (2012).

[26] Miguel A. González-Gay et al., Genetic Markers of Disease Susceptibility and Severity in Giant Cell Arteritis and Polymyalgia Rheumatica, 33 Seminars Arthritis & Rheumatism 38 (2003).

[27] Immunosenescence is the "decline in immunocompetence with advancing age, characterized by increased susceptibility to infection and tumor formation, decreased response to vaccination, and an increase in autoantibodies and monoclonal immunoglobulins." Immunosenescence, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=24933 (last visited Apr. 6, 2023).

[28] Kornelis Stephan Mario van der Geest, Senescence of The Adaptive Immune System in Health and Aging-Associated Autoimmune Disease, [Groningen]: Univ. of Groningen (2015).

[29] Petar Scepanovic et al., Human Genetic Variants and Age are the Strongest Predictors of Humoral Immune Responses to Common Pathogens and Vaccines, 10 Genome Med. 59 (2018).

23 at 4. Thus, according to Dr. Gershwin, it is the combination of environmental factors, which he contends include vaccination and genetics, that can cause GCA. Tr. 39-40.

To support vaccination as an environmental factor causing GCA, Dr. Gershwin opined that after vaccination, there is an expected production of cytokines and prostaglandins that activate dendritic cells. Tr. 26, 35-36, 58-59. They then turn naïve CD4 T cells into activated inflammatory T cells to produce inflammatory mediators. Tr. 26, 35-36, 58-59. Dr. Gershwin suggested GCA is a T cell-mediated disease, and the activation and maturation of dendritic cells is "one of the earliest steps in the pathogenesis of GCA." Pet. Ex. 23 at 3-4 (citing Pet. Ex. 53 at 1; Pet. Ex. 54 at 1).[30]

He further detailed this process and described what happens immunologically after receiving a vaccination. Tr. 48-49. First, the local injection of vaccination produces an "expected immune response." Tr. 26, 48. This includes the recruitment of cells, as well as the production and secretion of cytokines and prostaglandins in the blood. Tr. 26; see also Tr. 127-28. Next, "the susceptible population of dendritic cells [] located within [] susceptible vessels" become activated. Tr. 48-49; see also Tr. 26. Chemokines, which are produced by those dendritic cells, then attract the surrounding immune cells including macrophages and CD4+ T lymphocytes on the outside of the vessel, to infiltrate the vessel and cause inflammation. Tr. 26, 33, 36-37, 49, 53

Accordingly, Dr. Gershwin opined that "the CD4 T cells themselves become activated and they turn into inflammatory cells as opposed to their naïve CD4 phenotype, and they produce [] pro-inflammatory cytokines." Tr. 49. They turn into "Th1, Th17 cells, and those cells will further inflame and produce other inflammatory cells, again, bringing more cells into this process." Tr. 36-37; see also Tr. 35 (explaining the change of a naïve CD4 T cell to an inflammatory T cell can be seen in Pet. Ex. 50 at 3 fig.1 because those T cells are then differentiated into Th1 and Th17 cells); Pet. Ex. 23 at 4 (explaining that Th1 and Th17 cells "play an important role in GCA"). Dr. Gershwin contended that naïve T cells are now producing inflammation which "leads to further recruitment of activating cells, [] called bystander activation."[31] Tr. 35-36.

Dr. Gershwin opined GCA and PMR are "manifestations of the same underlying genetic/immunology disease and theories of pathogenesis of one can be extrapolated to the other." Pet. Ex. 108 at 2; see also Pet. Ex. 23 at 8. "PMR is due to an acute and persistent cytokine influence on the host vascular system." Pet. Ex. 108 at 2. Accordingly, he testified that

[30] Wei Ma-Krupa et al., Activation of Arterial Wall Dendritic Cells and Breakdown of Self-Tolerance in Giant Cell Arteritis, 199 J. Experimental Med. 173 (2004).

[31] Bystander activation is defined as "B cell stimulation with T cell help provided by a T helper cell responding to an unrelated antigen." Julius M. Cruse & Robert E. Lewis, Illustrated Dictionary of Immunology 119 (3rd ed. 2009).

the activation process for GCA is the same activation process for PMR with regard to vaccine causation. Tr. 57-59, 61.[32]

In support of his mechanistic theory, Dr. Gershwin cited Ly et al., which described the pathological process of GCA. Pet. Ex. 23 at 3; Tr. 32-35; Pet. Ex. 50 at 2-3. Ly et al. provided that dendritic cells become activated by an unknown stimulus "that might be a microbial antigen (viral or bacterial) or an autoantigen,"[33] and they recruit and activate CD4+ T lymphocytes and infiltrate the vessel. Pet. Ex. 50 at 2, 3 fig.1. The authors discussed possible unknown stimuli, including the "potential role of viruses and/or bacteria;" however, while a "large number of pathogens have been investigated," no association has been found with the "herpes virus, varicella virus, [] Epstein-Barr virus," cytomegalovirus, or human parvovirus.[34] Id. at 5. They further stated that "despite the large number of studies conducted so far, no infectious agent has been clearly identified to be associated with GCA, which does not favor the hypothesis that an infectious antigen could trigger the disease process." Id. Ly et al. did not suggest that vaccines play any role in triggering GCA.

Due to the lack of confirmation that an infectious agent triggers the illness, the Ly et al. authors suggested that the pathogenesis may be "an immune response directed toward an autoantigen." Pet. Ex. 50 at 5. An "alternative hypothesis" is that there is an autoantigen in the arterial wall, which "trigger[s] a specific immune response in GCA." Id. at 6.

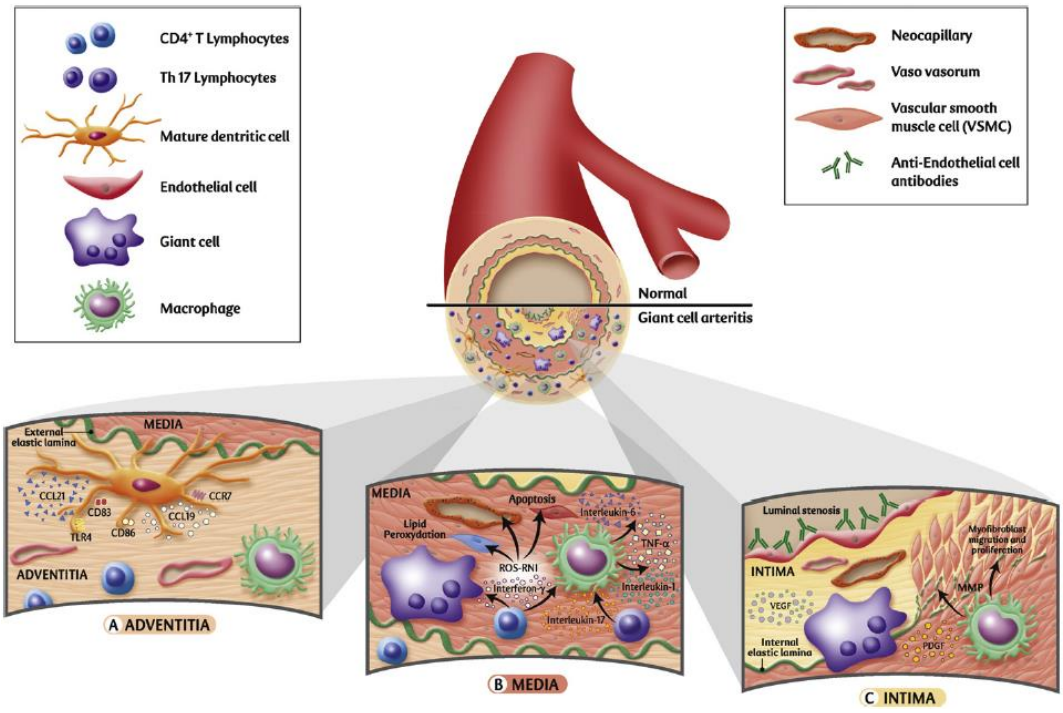
As described by Ly et al., once the T lymphocytes are activated, they undergo clonal expansion, producing interferon-γ and become Th1 and Th17 which promote and recruit macrophages. Pet. Ex. 50 at 3 fig.1. "Activated macrophages produce pro-inflammatory cytokines such as [tumor necrosis factor ("TNF")-α], [interleukin ("IL")-1], and IL-6, thus promoting local and systemic inflammation. They can fuse, form giant cells[,] and participate in the formation of granulomas." Id.; see also Tr. 49. The process is focused on the inner

[32] Dr. Gershwin testified, however, that "the pathology of PMR, exclusive of vaccination, is not a vasculitis, but it is thought to be a pro-inflammatory state." Tr. 57.

[33] An autoantigen is "an antigen that, despite being a normal tissue constituent, is the target of a humoral or cell-mediated immune response, as in autoimmune disease." Autoantigen, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=4923 (last visited May. 17, 2023); see also Julius M. Cruse & Robert E. Lewis, Illustrated Dictionary of Immunology 83 (3rd ed. 2009).

[34] "An association of cytomegalovirus with GCA was found by *in situ* hybridization," but was not confirmed by polymerase chain reaction in five other studies. Pet. Ex. 50 at 5. "Human parvovirus B19 (HPVB19) DNA was found in 7 of 13 biopsy-positive and 4 of 37 biopsy-negative GCA cases" and was confirmed in a larger study. Id. But four other studies failed to detect HPVB19 from patients with GCA. Id.

components of the affected vessels (the media and intima). Pet. Ex. 68 at 2.[35] Ly et al. illustrated these components:



Pet. Ex. 50 at 3 fig.1.

In addition to Ly et al., Dr. Gershwin also cited an older paper (1994) by Emilie et al.,[36] which showed that IL-6 serum levels are increased in GCA patients, and they postulated that "this cytokine may play a role in the systemic symptoms associated with [the] disease." Pet. Ex. 71 at 1. They also show that IL-6 is "produced by inflammatory cells of the GCA granulomas." Id. at 2. They did not discuss or describe any role of vaccinations in the cause of GCA. The primary takeaway from the article is that the finding of specific cytokines in granulomas may be associated with the systemic manifestations of GCA. See id. at 3, 7. Dr. Gershwin admitted that the "precise role of [] pro-inflammatory cytokines in GCA largely remains to be elucidated." Pet. Ex. 23 at 5.

[35] Annette D. Wagner et al., Interferon-γ-Producing T Cells in Giant Cell Vasculitis Represent a Minority of Tissue-Infiltrating Cells and Are Located Distant from the Site of Pathology, 148 Am. J. Pathology 1925 (1996).

[36] Dominique Emilie et al., Production of Interleukin 6 by Granulomas of Giant Cell Arteritis, 39 Hum. Immunology 17 (1994).

Dr. Gershwin also cited Hernández-Rodríguez et al.[37] in support of his theory. See Pet. Ex. 73 at 1. Like Emilie et al., Hernández-Rodríguez et al. examined the "systemic inflammatory response [] triggered by pro-inflammatory cytokines" including IL-1, IL-6, and TNF-α. Id. The goal of the study was to "investigate the relationship between the magnitude of cytokine expression in the lesions" and "the intensity of the systemic inflammatory reaction . . . and response to corticosteroid therapy." Id. at 1-2. While they did find pro-inflammatory cytokines were "expressed in temporal artery lesions" in patients with GCA, especially in granulomas, they did not discuss vaccinations or their role in pathogenesis of the disease. See id. at 6.

During the hearing, Dr. Gershwin referenced Hervé et al.[38] to explain how, in general, cytokines can be found in the sera after vaccination so as to cause symptoms beyond the local injection site. Tr. 127. "Once stimulated, the immune system sets off a complex series of innate immune events" such as "release of inflammatory mediators including chemokines and cytokines, activation of complement, and cellular recruitment." Pet. Ex. 137 at 2. The produced cytokines "act both locally . . . and may act systemically at distant organs." Id. at 4 fig.2. Based on this, Dr. Gershwin testified "cytokines, prostaglandins, chemokines, and other mediators are found in circulation and do have biologic effects." Tr. 127.

Often, he compared his proposed mechanism to the activation of the immune system by an infectious process in a genetically susceptible host, however, he acknowledged that there are no specific infections associated with GCA/PMR. Tr. 39-40, 43-46; Pet. Ex. 23 at 3.

In sum, Dr. Gershwin opined that the activation of the GCA process involves the activation of T cells and macrophages, which is "caused by the influence of endothelial dendritic cells, that initially become activated by circulating cytokines [and] prostaglandins produced during vaccination in a genetically susceptible host." Tr. 36; see also Tr. 53.

While he acknowledged that his proposed theory involved the activation of T cells, Dr. Gershwin did not explain what caused the activation of those T cells. And his testimony was sometimes confusing. He characterized GCA is an "autoimmune disease," but explicitly opined that molecular mimicry, which is often associated with autoimmune conditions, was not applicable. Tr. 40, 44, 47, 121-22. At other times, he stated that the process was "simply an activation of the immune system." Tr. 39, 43-44, 47.

Moreover, at times he opined that his theory was "driven by antigen," but at other times, he opined that it was not antigen specific. Tr. 26, 39; Pet. Ex. 23 at 4. He opined that the mechanism involved both the innate and adaptive immune system. Tr. 51-52. But he disagreed that it was primarily an adaptive immune response due to the formation of granulomas, and he

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[37] J. Hernández-Rodríguez et al., Tissue Production of Pro-Inflammatory Cytokines (IL-1β, TNFα and IL-6) Correlates with the Intensity of the Systemic Inflammatory Response and with Corticosteroid Requirements in Giant-Cell Arteritis, 43 Rheumatology 294 (2004).

[38] Caroline Hervé et al., The How's and What's of Vaccine Reactogenicity, 39 NPJ Vaccines 1 (2019).

explained that "[g]ranulomas are formed via macrophages and the innate immune system." Tr. 121. Dr. Gershwin reasoned if this process were solely an adaptive immune response, there would not be "granuloma formation throughout [the] disease." Id.

Although he opined that GCA was driven by an antigenic response, again, Dr. Gershwin did not describe what triggered T cell activation given his proposed theory. When pressured on cross-examination about how T cells were activated in his mechanistic theory, Dr. Gershwin opined that it is "most likely dependent on an antigen present with senescence," which he described as a "neoantigen." Tr. 121-22. The neoantigen could be within the blood vessel, or "an antigen that the body itself has but it requires the immune system to become activated to attack it." Tr. 122; see also Pet. Ex. 23 at 4 (explaining that GCA can be "driven by one or more antigen(s) that are enriched in temporal artery tissue" (citing Pet. Ex. 60 at 4-8)).[39]

Unlike Respondent's expert, Dr. Wilfong, however, Dr. Gershwin did not believe the mechanism was dependent on a specific vaccine or infectious agent. Tr. 121-22. And he acknowledged that no specific antigen has been identified as the trigger of GCA. Id.; Pet. Ex. 60 at 2, 5, 10; Pet. Ex. 68 at 2, 7-8. He cited Martinez-Taboada et al., which concluded that while GCA is a T cell mediated disease involving antigen recognition, the antigen is unknown. Pet. Ex. 60 at 2, 5, 10. However, neither Martinez-Taboada et al. nor Wagner et al., another article cited by Dr. Gershwin, suggested that the antigen at issue is a "neoantigen," created due to senescence, as suggested by Dr. Gershwin. See Pet. Exs. 60, 68. Further, the medical literature does not explain how vaccination could lead to the presence of local antigen within vessel wall tissues or respond to existing antigen in the vessels. See Pet. Ex. 23 at 4 ("[I]t is currently unclear how CD4+ T cells . . . orchestrate the formation of granuloma[s] and the activation of macrophages.").

Additionally, Dr. Gershwin explained that only a small number of T cells are antigen specific. Tr. 125, 128; see also Pet. Ex. 60 at 7, 9-10 (describing the T cell specificities involved in the antigen-specific response are only a "minor fraction" of the tissue infiltrating T cells); Pet. Ex. 68 at 2, 7 (same). He testified that "[o]nly a very small percentage of those cells are specific to the vaccine, the rest are all bystander cells." Tr. 125-26. Bystander cells "may not be antigen-specific, [] but could be very damaging and very inflammatory." Tr. 125; see also Tr. 129 (testifying that bystander activation means "that there would be T cells infiltrating that area that may not be antigen-specific"). Further, naïve T cells are "not necessarily recognizing antigen" and mature T cells "may have the ability to recognize antigen, but may be relatively nonspecific." Tr. 128. He concluded that the inflammation caused by T cells infiltrating the vessel in GCA is "probably both antigen-specific" and "antigen nonspecific, . . . meaning there's probably an autoinflammatory component to this in addition to [] whatever antigen specificity might be occurring here." Tr. 26.

Specific to PMR, Dr. Gershwin testified that PMR is "not a vasculitis," but a "pro-inflammatory state." Tr. 57. But he "speculate[ed] that PMR is temporal arteritis in the absence of senescent endothelial cells." Tr. 58. And he opined that the dendritic cells begin the process

[39] V. Martinez-Taboada et al., Recognition of Tissue Residing Antigen by T Cells in Vasculitic Lesions of Giant Cell Arteritis, 74 J. Molecular Med. 695 (1996).

that leads to inflammation with the "systemic manifestations of temporal arteritis without the local vessel changes." Id.

In support of his opinion that vaccinations may be associated with vasculitis conditions,[40] Dr. Gershwin cited Felicetti et al.,[41] who provided an overview of vasculitis reported in three databases, including the Vaccine Adverse Event Reporting System ("VAERS").[42] Pet. Ex. 23 at 7 (citing Pet. Ex. 125 at 1). Reports of vasculitis following vaccinations between 2003 and 2014 were reviewed. Pet. Ex. 125 at 1. Just more than half of the reports were in children. Id. at 2-3. The most common types of vasculitis reported were Henock-Schoenlein Purpura and Kawasaki Disease,[43] reported at 19.1% and 16.1%, respectively. Id. at 3. PMR made up 9.2% of the reports. Id. GCA was not specifically reported.[44] See id. at 3, 4 fig.1. The most commonly reported vaccine was the influenza ("flu") vaccine. Id. at 4 fig.2. Tetanus vaccines were reported but the number of reports appear to be very small, and the number does not appear to be specified. Id. Felicetti et al. did not discuss the Tdap vaccine specifically, and they did not mention any association between the Tdap vaccine and GCA or PMR.

Further, the case reports cited by Dr. Gershwin involved the flu vaccine, not the Tdap vaccine. Soriano et al. reported 10 cases of previously healthy individuals who developed GCA or PMR following the flu vaccine. Pet. Ex. 112 at 1; see also Pet. Ex. 127 at 2 (reporting cases of GCA and PMR after the flu vaccine);[45] Pet. Ex. 115 at 1 (reporting three cases of GCA/PMR

[40] While Dr. Gershwin opined GCA is a vasculitis, he testified "the pathology of PMR, exclusive of vaccination, is not a vasculitis, but it is thought to be a pro-inflammatory state." Tr. 57; see also Pet. Ex. 23 at 7 ("[PMR] is considered a vasculitis-related event.").

[41] Patrizia Felicetti et al., Spontaneous Reports of Vasculitis as an Adverse Event Following Immunization: A Descriptive Analysis Across Three International Databases, 34 Vaccine 6634 (2016).

[42] VAERS is a "national early warning system to detect possible safety problems in [] vaccines." About VAERS, https://vaers.hhs.gov/about.html (last visited May 17, 2023). "VAERS accepts and analyzes reports of adverse events (possible side effects) after a person has received a vaccination. Anyone can report an adverse event to VAERS. Healthcare professionals are required to report certain adverse events." Id.

[43] Kawasaki disease is "a syndrome of unknown etiology, . . . associated with vasculitis of the large coronary vessels." Kawasaki Disease, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=70488 (last visited Apr. 14, 2023).

[44] Temporal arteritis is noted in Figure 1 and 2 but it is difficult to discern the number of reports related to that condition. Pet. Ex. 125 at 4 figs.1-2.

[45] Eric Liozon et al., Giant Cell Arteritis or Polymyalgia Rheumatica After Influenza Vaccination: A Study of 12 Patients and a Literature Review, 20 Autoimmunity Reviews 102732 (2021).

after flu vaccination);[46] Pet. Ex. 117 at 1 (discussing the case of a 63-year-old man who developed PMR symptoms three weeks after flu vaccination);[47] Pet. Ex. 114 at 1 (reporting on a 76-year-old who developed GCA one week after flu vaccination);[48] Pet. Ex. 111 at 2-23 (reporting on a 70-year-old woman who developed GCA and PMR following the flu vaccine).[49]

Another paper, by Agger et al.,[50] reported on a cohort study which showed that the varicella zoster virus was "was associated with an increased incidence of GCA." Pet. Ex. 123 at 1. They suggested that the association might be caused by a "subacute or persistent arterial wall infection" due to the live attenuated virus vaccine,[51] leading to an arterial wall infection, or an immune response to the varicella zoster virus already present in the arterial walls, or a non-viral autoimmune reaction triggered by the vaccine. Id. at 4.

Dr. Gershwin acknowledged that the literature is primarily based on the flu vaccine rather than the Tdap vaccine, but argued that "the proof of principle is the same." Pet. Ex. 108 at 2. Further, he asserted that the flu vaccine "is the most common vaccination of senior citizens." Id. at 1. And given that GCA and PMR are "age-acquired disease[s]," he suggested that it was "not surprising" that many case reports involve the flu vaccine. Id.

Regarding the Tdap vaccine, Dr. Gershwin cited one case report by Saadoun et al.[52] Pet. Ex. 113. The article is in French, and only the abstract (summary) was translated to English. Id. at 1. Based on the summary, the only information available is that a 68-year-old woman developed GCA and PMR after a tetanus vaccination. Id. The authors "suggest[ed] the responsibility of vaccination in starting or reactivating systematic vasculitis." Id.

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[46] Reuven Mader et al., Systematic Vasculitis Following Influenza Vaccination – Report of 3 Cases and Literature Review, 20 J. Rheumatology 1429 (1993).

[47] M.A. Brown & J.V. Bertouch, Rheumatic Complications of Influenza Vaccination, 24 Austl. & N.Z. J. Med. 572 (1994).

[48] Carlos Perez et al., Giant Cell Arteritis After Influenza Vaccination, 160 Archives Internal Med. 2677 (2000).

[49] Makoto Wada et al., Giant Cell Arteritis with Polymyalgia Rheumatica Associated with Influenza Vaccination, 38 J. Dermatology 1099 (2011).

[50] William A. Agger et al., Increased Incidence of Giant Cell Arteritis After Introduction of a Live Varicella Zoster Virus Vaccine, 8 Open Forum Infectious Diseases (2020).

[51] There is no evidence here, however, that the vaccine at issue was a live attenuated vaccine.

[52] D. Saadoun et al., Vascularites Postvaccinales: À Propos de Trois observations, 22 Rev. Méd. Interne. 172 (2001).

To study the association of vasculitis with vaccination, the Brighton Collaboration[53] Vasculitis Working Group ("Working Group") was formed in 2014. Pet. Ex. 135 at 2. Petitioner filed a copy of their systematic review of the medical literature, authored by Bonetto et al.[54] Id. Ultimately 75 studies were reviewed by the Working Group. Id. at 1. In these, there were only two reports of vasculitis following the diphtheria-pertussis-tetanus ("DPT") vaccine. Id. at 4 fig.2. The specific type of vasculitis, however, was not reported. See id. at 4 fig.2, 5. There was also one case report of Kawasaki disease after the DPT vaccine. Id. at 6 tbl.1. The Working Group noted that the flu vaccine was the most often reported, particularly in the elderly, which "could be explained by the elderly representing a target population for [flu] vaccination." Id. at 9. They concluded that "[e]xisting literature does not allow establishing a causative line between vaccination and [vasculitis]," and they recommended further study. Id.

Dr. Gershwin also provided literature on the "rigorous" immune responses elicited by the Tdap vaccine to further support his theory. Pet. Ex. 108 at 1-2; see also Pet. Ex. 103 at 1 (emphasizing the "enormous degree of genetic variation" of immune responses because of numerous T cell variations). Van der Lee et al.[55] conducted a study to determine immunoglobulin G ("IgG") levels in 105 healthy adults after the Tdap booster vaccination. Pet. Ex. 119 at 6-7. They concluded that the Tdap booster resulted in increased levels of Th1, Th2, and Th17 cytokines. Id. at 9. Dr. Gershwin opined that the "data reflective of the robust cytokine release following the Tdap vaccine is consistent with the cytokine requirements of PMR." Pet. Ex. 108 at 2. However, the study was conducted on healthy adults ages 25 to 29 years of age, and it is not clear whether the results would translate to an older population. See Pet. Ex. 119 at 1.

ii. Althen Prong Two

Dr. Gershwin agreed with Petitioner's treating physicians that the appropriate diagnoses were GCA and PMR. Pet. Ex. 23 at 2; Tr. 23. He opined that Petitioner's Tdap vaccine more likely than not caused his GCA and PMR through the mechanism described above—the activation of the immune system leading to an inflammatory response. Pet. Ex. 23 at 4-7; Pet. Ex. 108 at 1; Tr. 15, 23, 26. While he conceded "[t]here is no smoking gun," he opined it is the "plausible explanation" for Petitioner's GCA and PMR "in the absence of other inciting factors." Pet. Ex. 108 at 2. He described the mechanism as "similar to that [of] an infectious agent," that

[53] The Brighton Collaboration is an international community made up "individuals and organizations concerned with immunization safety or with associated medical and methodological aspects" aimed to "[e]nhance the science of vaccine research, by providing [standardized], validated and objective methods for monitoring safety profiles and benefit to risk ratios of vaccines." About, Brighton Collaboration, https://brightoncollaboration.us/about/ (last visited May 18, 2023).

[54] Caterina Bonetto et al., Vasculitis as an Adverse Event Following Immunization – Systematic Literature Review, 34 Vaccine 6641 (2016).

[55] Saskia van der Lee et al., Robust Humoral and Cellular Immune Response to Pertussis in Adults After a First Acellular Booster Vaccination, 9 Frontiers Immunology 681 (2018).

is, "similar to that of an environmentally induced disease[] in a genetically susceptible host." Tr. 46. Dr. Gershwin opined that Petitioner "would not have developed GCA and PMR had he not been vaccinated on that date." Id.

He explained the logical sequence of cause and effect began with Petitioner's genetic susceptibility. Tr. 45, 50, 53. He did not, however, identify any genetic susceptibility specific to the Petitioner. Further, it does not appear that Petitioner had HLA testing, or any other genetic tests to determine whether he had any predisposition to GCA.[56] Nevertheless, Dr. Gershwin opined that given Petitioner's "unique genetic signature, there would be an abnormal and excessive response following the Tdap vaccine,[57] which would produce the symptomatology that he experienced following vaccination, and which is characteristic of . . . PMR." Pet. Ex. 108 at 2. The cytokines and prostaglandins produced by the Tdap vaccine activated dendritic cells, attracted immune cells, and turned the naïve CD4 cells into inflammatory cells. Tr. 53. That impacted Petitioner's vessels by swelling, impeding oxygen delivery, and by recruiting macrophages that continued to recruit bystander cells, "all of which [] further inflame[d] and further impede[d] blood circulation, producing the inflammation, which in [Petitioner's] case was rapidly resolved by giving corticosteroids." Tr. 54; see also Tr. 22, 31 (stating Petitioner responded well to steroids, consistent with a vasculitis).

According to Dr. Gershwin, Petitioner's aches and pains in his neck, jaw, knees, and hip and stiffness throughout his body 19 days after vaccination resulted from this inflammatory process. Pet. Ex. 23 at 1; Tr. 16, 54. He further opined that "[t]he presence of the markers of inflammation, namely the elevated [ESR and CRP], and ultimately the positive biopsy and response to steroids" confirmed this. Tr. 16, 54. He explained the pathogenesis of PMR, as described above, can explain Petitioner's fatigue and polyarthralgias, as well as the elevation of acute phase reactants such as ESR. Pet. Ex. 108 at 2; see also Tr. 17. Dr. Gershwin did not find it unusual that Petitioner also developed sixth nerve palsy. Tr. 17.

Additionally, Dr. Gershwin acknowledged that both Petitioner's treating neurologist and rheumatologist noted that Petitioner recently received the Tdap vaccine. Pet. Ex. 23 at 1; Tr. 46, 55. He agreed with the neurologist that Petitioner had an inflammatory process involving the cranial nerve, consistent with GCA. Tr. 21.

Finally, Dr. Gershwin opined that Petitioner had "no other previous environmental factors that preceded the development of his [GCA and] PMR." Pet. Ex. 108 at 2.

iii. Althen Prong Three

Dr. Gershwin opined that GCA/PMR symptoms can begin to develop "within a couple of days" of vaccination, consistent with his proposed mechanism of an innate immune response.

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[56] For genetic susceptibility factors that have been suspected to increase the risk of GCA, see Pet. Ex. 50 at 6 tbl.2.

[57] This statement contradicts Dr. Gershwin's hearing testimony where he opined that Petitioner "had a normal response to the Tdap vaccine." Tr. 26.

Tr. 55. He explained that innate immunity progresses over time but typically occurs "within a period of six weeks." Id. Here, Dr. Gershwin agreed that Petitioner developed symptoms 19 days after receiving the Tdap vaccine. Tr. 53.

Then Dr. Gershwin talked about the time frame for activation of the adaptive immune system. The activation of T cells following vaccination tends to "follow the typical pattern of adaptive immune response, i.e., an initial exposure is followed by a lag phase, then a peak in the response . . . at about one to weeks, that eventually settles back down." Pet. Ex. 131 at 4. Dr. Gershwin testified "T cells respond within days, certainly by three, five, seven days, you'll start to get pretty good T cell responses. By 19 days, if the stimulus is potent enough, you will get very significant T cell responses." Tr. 55. Thus, he opined 19 days was "well within the kinetics of a T cell response." Id.

Dr. Gershwin cited case reports to support his opinion that 19 days is an appropriate temporal association between vaccination and injury for the proposed mechanism. Pet. Ex. 23 at 7; Pet. Ex. 108 at 1; Tr. 16, 55. Dr. Gershwin testified generally that the latency time documented in case reports is three days to six weeks. Tr. 46, 55-56. For example, Felicetti et al. found the temporal relationship between a vaccine and a "vaccine induced vasculitis is deemed to be in the range of one to six weeks." Pet. Ex. 125 at 2. Further, Soriano et al. described a patient who developed GCA symptoms 20 days post-vaccination. Pet. Ex. 112 at 1. They also reported 10 patients diagnosed with GCA/PMR within three weeks to three months of vaccination. Id. at 2 tbl.1; see also Pet. Ex. 115 at 1 (discussing case reports of two individuals who developed GCA/PMR within two weeks of receiving a flu vaccine); Pet. Ex. 117 at 1 (discussing the case of a 63-year-old who developed PMR symptoms three weeks after flu vaccination).

2. Respondent's Expert, Dr. Erin Wilfong[58]

a. Background and Qualifications

Dr. Wilfong is board certified in internal medicine and rheumatology. Resp. Ex. A at 2; Resp. Ex. B at 1. After receiving her M.D. and Ph.D. in Chemistry from Duke University, she completed an internal medicine residency at Johns Hopkins Hospital, and a rheumatology fellowship at the University of California, San Francisco. Resp. Ex. A at 1; Resp. Ex. B at 1. She is currently a pulmonary and critical care fellow at Vanderbilt University where she runs a research lab and is an attending physician in the medical intensive care unit. Resp. Ex. A at 1; Resp. Ex. B at 1; Tr. 63. She has treated approximately 10-15 patients with GCA "at various points in their course" during her fellowship. Tr. 93. Dr. Wilfong has won numerous awards, completed various research projects, and co-authored several publications. Resp. Ex. A at 3-6.

b. Opinion

[58] Dr. Wilfong submitted two expert reports in this matter and testified at the hearing on September 27, 2022. Resp. Exs. B-C; Tr. 62.

Dr. Wilfong agreed that Petitioner has GCA and PMR. Resp. Ex. B at 3; Tr. 66. However, Dr. Wilfong disagreed that there is a causal relationship between the Tdap vaccine and GCA or PMR. Resp. Ex. B at 3-4.

i. Althen Prong One

Dr. Wilfong opined that Dr. Gershwin's theory is not sound or reliable for a number of reasons, including that his theory failed to explain how the T cells are activated. Resp. Ex. B at 3-7; Tr. 68-70. Additionally, she raised concerns about the fact that no antigen has been identified as playing a causal role in GCA, she disagreed with the role of cytokines, and she disagreed with how senescence was portrayed in the theory.[59] Resp. Ex. B at 3-7; Tr. 68-70. Lastly, she asserted that there is a lack of supportive evidence associating the Tdap vaccine with GCA/PMR. Resp. Ex. B at 3-7; Resp. Ex. C at 1-2.

Regarding the first criticism, Dr. Wilfong explained that T cells "start as naïve T cells, they are exposed to [] antigen-presenting cell[s] that [] present[] a peptide, and then they undergo maturation . . . to recognize [a] specific antigen, or a cross-reacting antigen." Tr. 98. She further explained that "T cells are antigen-specific," and that "both T and B cells are directed against antigen." Id. Dr. Wilfong agreed with the general pathophysiology of GCA as illustrated by Ly et al. Tr. 115; see Pet. Ex. 50 at 3 fig.1. She agreed with the description of the GCA process and the activation of T cells and macrophages set forth by Ly et al. Tr. 97. Her disconnect with Dr. Gershwin's theory, however, was how the T cells were activated. See Tr. 73.

Dr. Wilfong testified "it is theoretically possible" that an infection could trigger GCA/PMR, but that mechanism would involve molecular mimicry or cross-reactivity. Tr. 95, 111-12 (stating that infections "likely can" trigger GCA/PMR through an antigen-specific adaptive response "but which infection does it is unknown"). But she did not believe that vaccines could trigger GCA/PMR because she was not aware of "any molecular mimicry that would lead to that antigenic crossover." Tr. 95-96.

Dr. Gershwin described GCA/PMR as both "autoimmune" and "autoinflammatory" illnesses. Tr. 40, 125 (referring to GCA as autoimmune); Tr. 26, 39 (referring to GCA as autoinflammatory). In response, Dr. Wilfong defined the terms and testified that there is an important distinction between these two mechanisms of illness. Tr. 106. She defined autoimmunity as "recognition of self-antigen." Id. And she defined autoinflammatory as "immune dysregulation," which she explained tends to be more cytokine mediated. Id. She viewed these as different disease pathways, with autoimmunity, applicable here, generally requiring T cell antigen-specific cross-reactivity (molecular mimicry). Tr. 107.

Dr. Wilfong agreed with the notion that GCA/PMR has a genetic predisposition. Tr. 95. She agreed generally that there is an unknown environmental trigger thought to contribute to the development of autoimmune and rheumatic diseases, such as GCA/PMR. Id.; Resp. Ex. C at 1. She also agreed that GCA and PMR "likely represent different manifestations of the same

[59] Dr. Wilfong offered criticism of other aspects of Dr. Gershwin's opinions, but the undersigned focuses on the most important aspects of her opinions.

underlying disease process." Resp. Ex. B at 3. But she testified that the way vaccines lead to autoimmunity is through "[molecular] mimicry or immune disactivation." Tr. 96. And she proposed that GCA and PMR are "trigger[ed] [by] a specific antigenic response." Id.; see also Tr. 106-07.

To support her position that T cells and the mechanism for activating those T cells are antigen-specific, she explained how T cells recognize and develop cellular responses. Tr. 98. She testified that individuals are born with a limited number of T cells that change and mature and the "T cell learns to recognize a single antigen very, very, very well." Tr. 76. T cells start out naïve, are "exposed to an antigen-presenting cell that is presenting a peptide, and then they undergo maturation . . . to recognize that specific antigen, or a cross-reacting antigen." Tr. 98; see also Tr. 100. The antigen-presenting cell (the dendritic cell) "will load a peptide onto its surface [and] it will be recognized by the T cell receptor" to activate those T cells. Tr. 98; see also Tr. 68-69. "[T]he T cell receptor is what [] detects antigen, and what recognizes antigen." Tr. 99. She acknowledged that cytokines released by the dendritic cell can also stimulate and "polarize that T cell and help [it] know what it wants to be when it grows up." Tr. 100; see also Tr. 69 (stating cytokines and other components are "second signals for T cell activation"). Dr. Wilfong further acknowledged the "enormous variation" of T cells but maintained that mature T cells are antigen-specific. Tr. 97-98, 101.

In addition to the role of T cells, Dr. Wilfong testified that B cells are also antigen-presenting cells, and are "one of the most potent activators of CD4 T cells" by presenting their antigen. Tr. 86; see also Tr. 99-100. She cited van der Geest, who described B cell abnormalities in GCA, indicating "that B cells were actually involved both at the site of inflammation as being potentially a local source of inflammation, but also in the secondary lymphoid tissue." Tr. 86-87; see also Pet. Ex. 130 at 121. She opined "this is a very specific antigen presentation . . . because B cells . . . present a single thing." Tr. 87.

Further, in addition to disagreeing with Dr. Gershwin about the fact that T cell activation would necessarily require a specific antigen, Dr. Wilfong explained that a specific antigen is not known based on the current state of available knowledge. See Tr. 115 (testifying that Ly et al. does not mention a specific antigen or antigens and their role in activating the GCA process because "we don't know what that antigen is"); Tr. 116 (testifying that at the current state of scientific knowledge, the "antigen is not known"); see also Resp. Ex. B, Tab 1 at 15 (noting that vasculitis such as GCA is driven by a "T cell response to a specific but unknown antigen");[60] Pet. Ex. 60 at 9-10 ("The nature of the antigen recognized by the T cells is unclear."); Pet. Ex. 68 at 8 (noting research has "not found any sharing of TCR molecules among different patients that would indicate the existence of a common antigen").

Next, Dr. Wilfong addressed the issue of cytokines. See Resp. Ex. C at 2. She testified that only "low amounts" of cytokines are released from vaccination and enter into the circulatory system to travel throughout the body. Tr. 110-11. Dr. Wilfong posited that if Dr. Gershwin's

[60] David B. Hellmann, Giant Cell Arteritis, Polymyalgia Rheumatica, and Takayasu's Arteritis, in Kelley and Firestein's Textbook of Rheumatology 1520, 1533 (Gary S. Firestein et al. eds., 10th ed. 2017).

theory is correct, the cytokine elevation "should match what is seen in GCA and PMR, and it does not." Tr. 88. For example, she noted van der Geest "did not find any difference in the serum of GCA or PMR patients of IL-1β or TNF-α" compared to control patients, but they did find IL-6 differences. Tr. 87 (citing Pet. Ex. 130 at 162 tbl.1). "[T]hey did not find interferons or interleukins or TNF [] elevated in their cohort of [GCA]." Id. Dr. Wilfong opined this is inconsistent with Dr. Gershwin's position that elevated cytokines from vaccination can trigger GCA. Tr. 87-88.

Similarly, Dr. Wilfong testified that Petitioner did not file any literature establishing that the Tdap vaccination specifically results in elevated cytokine levels, particularly TNFs and interferons. Tr. 88. Dr. Wilfong alleged there was no evidence presented to support the contention that "cytokines are [] released by the tetanus vaccine or what their levels are." Tr. 111. She noted van der Lee et al., cited by Petitioner, investigated secreted cytokines after T cell stimulation, not plasma or serum cytokine levels post-vaccination. Resp. Ex. C at 2 (citing Pet. Ex. 119). Dr. Wilfong cited Ovsyannikova et al.,[61] which studied "the role of cytokines in defining and predicting humoral response to measles immunization." Resp. Ex. C, Tab 4 at 6. They found "no correlation between cytokine production . . . after [] stimulation and circulating levels of plasma cytokines." Id. at 1. Dr. Wilfong explained that "lymphocyte cytokine responses do not necessarily correlate with plasma cytokine responses post-vaccination." Resp. Ex. C at 2. Therefore, she opined that there is no evidence of "an acute inflammatory state arising from [Tdap] vaccination." Id.

Dr. Wilfong's next issue regarding cytokines related to Dr. Gershwin's reliance on Emilie et al., which discussed the role of cytokines, especially IL-6, in the formation of GCA granulomas. See Tr. 78. Emilie et al. showed "increased serum concentrations of IL-6 are at least partly [the] result from the local production of this mediator within the inflamed arteries." Tr. 78-79 (quoting Pet. Ex. 71 at 3). Dr. Wilfong explained that the study showed that "inflammation came from the granuloma, and from the inflamed vessels, and then lead to the distant systematic symptoms of GCA." Tr. 79. According to Dr. Wilfong, this is not Dr. Gershwin's position. Id. Instead, he opined that "the vaccine led to the systematic inflammation, [which then] led to the granulomas." Id. Dr. Wilfong suggested this is a "key difference" between what Emilie et al. showed and Dr. Gershwin's theory relative to "where the cytokine [] originat[es]." Id.

Additionally, although Dr. Wilfong agreed that the immune system ages, she disagreed that there was evidence to support Dr. Gershwin's idea that "aging" contributes to the mechanism by which vaccines can triggers GCA. Tr. 91.

Regarding Dr. Gershwin's opinion that his proposed mechanism is analogous to that following infection, Dr. Wilfong disagreed that Agger et al. supported such. See Tr. 82. Dr. Wilfong opined that Agger et al. reported cases of "post-vaccine GCA [which] occurred months after the varicella vaccination" and questioned whether there was an association between the live varicella virus and the occurrence of GCA. Tr. 82-83. She testified the authors' conclusion was

[61] Inna G. Ovsyannikova et al., Cytokine Production Patterns and Antibody Response to Measles Vaccine, 21 Vaccine 3946 (2003).

that "acute [varicella zoster virus] infection does not appear to cause post-vaccination GCA." Tr. 83 (quoting Pet. Ex. 123 at 4). Further, instead of acute infection as the mechanism of causation, Dr. Wilfong explained that Agger et al. "postulated that [the cause was] either due to [] chronic arterial wall inflammation from varicella, or that the varicella vaccine [was] driving an immune response to the [varicella zoster virus] that [was] already present." Id. She explained that these mechanisms require antigen specificity. Tr. 83-85.

Regarding Soriano et al., which reviewed literature on GCA and PMR following flu vaccination, Dr. Wilfong took issue with the study because it included any patient who developed GCA/PMR within three months of vaccination. Tr. 79-80. Because this risk window was so long ("a quarter of the year"), any case of GCA during that time frame was considered to be "related to the vaccine." Tr. 108; see Pet. Ex. 112 at 1. She believed that equating a temporal association with causation was a "a fundamental flaw" in Soriano et al. Tr. 109.

Finally, she averred that several of Dr. Gershwin's references are not supportive because they do not mention vaccines containing tetanus, diphtheria, or pertussis. Resp. Ex. B at 4-6. Dr. Wilfong opined that case reports after the flu vaccine "do not support a causal relationship for the Tdap vaccine." Resp. Ex. C at 2. She opined that "literature on one vaccine cannot be automatically extrapolated to another." Id.; see also Resp. Ex. B at 7; Tr. 81-82 (testifying to the difficulty of accepting that "just because one vaccine can do something, something else can do it[] too"). Moreover, she suggested that if Tdap had a "significant association" with GCA/PMR, it would have been adequately reported since the Tdap vaccine was recommended to be administered to all individuals above the age of 12 years, including those above the age of 65 years "irrespective of occupation or contact with an infant." Resp. Ex. C at 2. She cited Bonetto et al. for the conclusion that existing literature does not establish a causative link between vaccines and vasculitis. Tr. 75; Resp. Ex. B at 7; Resp. Ex. C at 2; see Pet. Ex. 135 at 2. Thus, Dr. Wilfong concluded that "[n]o [] studies have purported a link between the Tdap vaccine and [PMR] or [GCA]." Resp. Ex. B at 7.

ii. Althen Prongs Two and Three

Dr. Wilfong agreed with Dr. Gershwin that Petitioner developed GCA/PMR in the fall of 2016. Resp. Ex. B at 3. She opined that Petitioner's myalgias/arthralgias were associated with PMR, and the jaw pain/claudication was "more likely than not" related to GCA. Id. Moreover, she agreed that the temporal biopsy confirmed Petitioner's GCA diagnosis, and she agreed that there is an association between GCA and PMR. Id.

Dr. Wilfong did not, however, agree that Petitioner's treating physicians provided statements supportive of causation. In her records, Dr. Kiehn stated "new onset in August 2016 [two] weeks after had Tdap, suspect related to this (reactive) but could also just be onset of new inflammatory arthritis." Pet. Ex. 1 at 10. Regarding Dr. Kiehn's note questioning whether Petitioner's GCA could be related to Tdap or a new onset of inflammatory arthritis, Dr. Wilfong viewed this as Dr. Kiehn statement "questioning" whether the vaccine "could be related." Tr. 70. To her, this was a statement of "differential diagnosis" and not an opinion as to causation. Tr. 70-71. "Differential diagnoses are usually broad and are not binding." Tr. 71. Dr. Wilfong explained that "just because something is [a] differential diagnosis does not mean that it is more

likely than not the cause." Id. Dr. Wilfong also explained that "reactive arthritis" is a condition distinct from GCA/PMR and "is typically related to molecular mimicry." Id. In summary, she did not find these statements by Dr. Kiehn to be supportive of causation. Id.

Similarly, Dr. Wilfong believed Dr. Katznelson's assessment that Petitioner's condition might be a hypersensitivity reaction to the vaccine was "hypothetical." Tr. 71-72. When determining the differential diagnosis, Dr. Katznelson "imagine[d] some sort of hypersensitivity reaction after the pertussis vaccine [was] [] possible." Pet. Ex. 3 at 116. Dr. Wilfong did not believe Dr. Katznelson's statement was an opinion in support of causation. Tr. 71-72.

Dr. Wilfong agreed "there is a temporal correlation between the Tdap vaccine and the onset of [Petitioner's] PMR symptoms," but she maintained that "there is no evidence of a causal relationship between the Tdap vaccine and [GCA/PMR]." Resp. Ex. B at 7; see also Tr. 89-90.

IV. DISCUSSION

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, Petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

B. Causation

To receive compensation through the Program, a petitioner must prove either (1) that he suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that he suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Petitioner must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because Petitioner does not allege he suffered a Table Injury, he must prove a vaccine he received caused his injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d. 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether a petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in his favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor).

Testimony that merely expresses the possibility—not the probability—is insufficient, by itself, to substantiate a claim that such an injury occurred. See Waterman v. Sec'y of Health & Hum. Servs., 123 Fed. Cl. 564, 573-74 (2015) (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

V. CAUSATION ANALYSIS

A. Althen Prong One

Under Althen Prong One, Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support his theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds Petitioner failed to provide preponderant evidence of a sound and reliable theory to explain how the Tdap vaccination can cause GCA or PMR. There are several reasons for this finding.

Both experts agree generally that while the process is not understood, the pathogenesis of GCA has been described and illustrated by Ly et al., which provides that dendritic cells "act as antigen-presenting cells, recruiting and activating CD4+ [toll-like receptors]." Pet. Ex. 50 at 3 fig.1. Dr. Gershwin agrees that there is T cell activation. Dr. Gershwin also agrees that Ly et al. and others suggest that the dendritic cells are activated by a viral or bacterial pathogen, or "by an autoantigen."[62] Id. at 2.

[62] Ly et al. also cite studies and make a number of references to dendritic cells' role as "critical" antigen-presenting cells. Pet. Ex. 50 at 2-3, 3 fig.1.

Because Dr. Gershwin said his theory was not driven by any specific antigen and also did not involve molecular mimicry, the weakness of Dr. Gershwin's theory is that he does not adequately explain how the vaccine, or the antigens in the vaccine, activate the T cells which, in turn, trigger GCA. As such, his theory fails to address the fundamental question of what triggers the T cell activation, as asked by Dr. Wilfong.

When pressed on cross-examination, Dr. Gershwin ultimately introduced a new step in his mechanistic theory, the formation of a neoantigen due to senescence. He speculates that his theory is "most likely dependent on an antigen present with senescence that we ought to call a neoantigen once it is finally identified." Tr. 122. He explained that a neoantigen is "an antigen that the body itself has, but it requires the immune system to become activated to attack it." Tr. 122. Neoantigen is defined by Dorland's Medical Dictionary as "a new antigenic determinant, such as a tumor-associated antigen, that is formed when a protein is modified by metabolic processes or that emerges when a conformational change exposes a previously unexpressed epitope." Neoantigen, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/Dorland/definition?id=33398 (last visited May 3, 2023). A neoantigen may also be "produced by the union of a xenobiotic with a self-protein." Julius M. Cruse & Robert E. Lewis, Illustrated Dictionary of Immunology 527 (3rd ed. 2009).

In summary, Dr. Gershwin proposes that T cell activation is triggered by a neoantigen, or "a new antigenic determinant," which Dr. Gershwin suggests occurs due to senescence or aging. However, Ly et al. and the other medical literature cited by Dr. Gershwin does not support the idea that a new antigenic determinant is created due to senescence.

Of the medical literature filed by Petitioner, and cited during the hearing by Dr. Gershwin, Ly et al. appears to be the most up-to-date and comprehensive summary of what is known about GCA and its pathogenesis to date. Ly et al. explains that dendritic cells become activated by an unknown stimulus "that might be a microbial antigen (viral or bacterial) or an autoantigen." Pet. Ex. 50 at 2. This unknown stimulus, which might be an antigen, in turn activates CD4+ T lymphocytes. Id. at 2, 3 fig.1. While the authors of Ly et al. observe that GCA occurs in an older population (over 50 years of age), they do not discuss any process whereby aging, or senescence, creates a neoantigen, or new antigen, that "the body itself has," or that such neoantigen triggers the pathogenesis of GCA/PMR. See Tr. 122; Pet. Ex. 50.

In the mouse model study discussed in Ly et al., dendritic cells were thought to be "critical antigen-presenting cells in GCA." Pet. Ex. 50 at 2. While the dendritic cells are thought to be in the arterial vessel walls, the authors of Ly et al. suggest that an antigen or autoantigen triggers the disease. Id. Ly et al. does not propose the idea of a neoantigen, or that aging creates the antigen responsible for triggering the disease.[63]

[63] Ly et al. does reference "neoangiogenesis," "neocapillaries," "neovascularization," and "neointimal cells," but these relate to the "vascular remodeling [that] corresponds to a maladaptive response that contributes to intimal hyperplasia and vascular lumen occlusion" in the illness, concepts that relate to vessel injury and obstruction in GCA as well as vascular remodeling. Pet. Ex. 50 at 4.

Moreover, Ly et al. summarize studies that have examined the role of viral or bacterial triggers of GCA and conclude that "despite the large number of studies conducted so far, no infectious agent has been clearly identified to be associated with GCA, which does not favor the hypothesis that an infectious agent could trigger the disease process, activate [dendritic cells,] and initiate vascular inflammation." Pet. Ex. 50 at 5. This is significant because Dr. Gershwin opined that his proposed mechanism was like that of an infection. If infection has not been found to be casually associated with GCA, then the immune process described by Dr. Gershwin, applicable to how infections trigger the immune system, is not a good fit to explain the pathogenesis of the illness.

Ly et al. also considered whether GCA is an autoinflammatory disease, as some mouse models studies have indicated. However, in GCA, there is "the absence of giant cells in aortic lesions," which the authors consider to be a "major difference." Pet. Ex. 50 at 7. Thus, while GCA shares some characteristics of autoinflammatory illnesses such as "the major implication of innate immunity and IL-1 function disturbances," due to key distinctions, Ly et al. does not definitively conclude that it is an autoinflammatory disease. Id. Dr. Gershwin, however, at times described GCA as autoinflammatory. Tr. 26, 39.

The other articles cited by Dr. Gershwin also do not support his theory. González-Gay et al. discusses genetic markers in GCA/PMR. In their conclusions, the authors question whether the conditions are "related to the aging process and due to loss of immune-homeostasis" and recommend additional research to address the question, but they do not conclude that aging leads to the development of a neoantigen capable of triggering the illness. Pet. Ex. 38 at 8.

In their paper about PMR, Falsetti et al. discuss "immunosenescence" as "an adaptive and innate immune deregulation in the elderly." Pet. Ex. 124 at 4. But they do not hypothesize that immunosenescence can lead to the formation of a neoantigen, or new antigen, capable of triggering T cell activation.

Van der Geest discusses senescence of the adaptive immune system and age associated immune disease. Pet. Ex. 130. He does not suggest, however, that immunosenescence leads to a neoantigen or a new antigen, that leads to T cell activation so as to cause GCA/PMR.

The second problem with Dr. Gershwin's opinions is that he used inconsistent and contradictory terms, contributing to confusion about his proffered mechanism. For example, he testified that the inflammation caused by T cells infiltrating the vessel in GCA is "probably both antigen-specific, but also [] probably antigen nonspecific as well, meaning there's probably an autoinflammatory component to this in addition to [] whatever antigen specificity might be occurring." Tr. 26. He also testified that his mechanism was a "pro-inflammatory response" that was "driven by an antigen." Tr. 39. In other instances, however, he referred to GCA/PMR as an autoimmune disease. Tr. 40. And he cited Bonetto et al. for the proposition that vasculitis may be a complication of autoimmune dysregulation. Tr. 41. Overall, Dr. Gershwin's opinions were difficult to follow.

In sum, based on his reports and testimony, Dr. Gershwin offers a theory that implicates both the innate and adaptive immune system, is both autoinflammatory and autoimmune in

nature, and includes a component of immune dysregulation (immunosenescence). Dr. Gershwin's approach of casting a broad net renders his opinions less persuasive on the whole.

While it may not be inappropriate to offer several alternative causal theories in support of vaccine causation, Petitioner's approach of identifying a handful of theories plus a novel concept (neoantigen) which is not supported by literature of other evidence reduces the persuasiveness of the opinions offered. See Baron v. Sec'y of Health & Hum. Servs., No. 14-341V, 2019 WL 2273484, at *17 (Fed. Cl. Spec. Mstr. Mar. 18, 2019) ("Although Petitioners . . . do not need to provide the specific components of the mechanism by which the vaccine[] at issue can cause [the alleged injury], they do need to propose something more than taking a vague 'kitchen sink' approach and listing eleven mechanisms that have been previously submitted in the Program for claims of vaccine-caused injury with various degrees of success. Petitioners have listed many possibilities but have not identified a sound and reliable explanation that can be applied to the vaccines and injury in this case.").

The third reason that the undersigned finds that Petitioner has not met his burden of proof is due to the lack of evidence that the Tdap vaccine can cause GCA/PMR. In the medical literature filed herein, there is one case report of GCA/PMR following Tdap or tetanus vaccination. It was reported by Saadoun et al., but only the summary was filed in English. The summary stated that a 68-year-old woman developed GCA and PMR after a tetanus vaccination. Due to the lack of factual information, diagnosis cannot be verified. Further, onset was not stated. Thus, it is difficult to determine whether this report is accurate or reliable.

The Working Group reported two cases of vasculitis following the DPT vaccine, however the type of vasculitis was not reported, and therefore, one cannot determine whether the diagnosis in those cases was GCA/PMR. Additionally, there are no meaningful facts provided about the two cases, making it difficult to discern whether the information is reliable.

While the undersigned generally finds case studies may provide some evidence of causation, due to the lack of factual information, the three case reports here do not provide foundational support or other basic indices of reliability. Clinical course, onset, and diagnosis cannot be verified, and thus, these case reports do not constitute sufficient evidence upon which to conclude that the Tdap vaccine can cause GCA/PMR.

Petitioner need not make a specific type of evidentiary showing or require identification of a specific antigenic trigger for an immune mediated pathology to prove that a theory is sound and reliable by preponderant evidence. Given the state of current scientific knowledge, there is no way that a petitioner could satisfy such a requirement. Particularly here, where Dr. Wilfong admitted that a specific antigen is not known based on the current state of available knowledge.[64] Further, requiring proof of the identify of a specific antigen to prove causation would require scientific certainty, which is a bar too high. See Knudsen, 35 F.3d at 549 (explaining that "to

[64] See Tr. 115-16 (testifying that at the current state of scientific knowledge, the antigen referred to in Ly et al. and its role in activating the GCA process is "not known"); Resp. Ex. B, Tab 1 at 15 (noting that vasculitis such as GCA is driven by a "T cell response to a specific but unknown antigen").

require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program").

However, based on the current understanding of GCA/PMR as described in the literature filed herein, Dr. Gershwin's proposed mechanism falls short for all of the reasons that have been discussed above, and primarily, he interjects the idea of a "neoantigen" that is not referenced or supported by the medical literature or any other evidence. In fact, none of the medical literature filed has identified any known cause of GCA, let alone any mention of a neoantigen. See, e.g., Pet. Ex. 12 at 7 (concluding that both GCA and PMR "are a result of an unknown causative factor (or factors)"); Pet. Ex. 53 at 1 (stating that "[i]t is not known how T-cell activation in the arterial wall is induced"); Pet. Ex. 71 at 1 (describing GCA as having an unknown etiology); Resp. Ex. B, Tab 1 at 1, 3, 5, 15 (iterating "the exact trigger of the adaptive immune response in GCA is not known"); Pet. Ex. 8 at 10 (noting that with regards to GCA, the question remains how an "antigen-driven immune response in which a small proportion of antigen-specific T cells specifically recognize the antigen" leads to tissue pathology); Pet. Ex. 50 at 2 (noting that "the key mechanisms involved in vascular remodeling that lead to luminal occlusion remain unidentified in GCA"); Pet. Ex. 54 (providing generally that the nature of the events leading to GCA remains elusive).

Moreover, Petitioner's case reports of vasculitis associated with vaccination generally involve the flu vaccination, which Petitioner did not receive. Therefore, the relevance of these case reports is unclear as case reports about one vaccine cannot automatically be imputed to a different vaccine, particularly when the mechanism offered has not been suggested as to the vaccine at issue. "An expert may 'extrapolate from existing data,' and use 'circumstantial evidence,' [b]ut the reasons for the extrapolation should be transparent and persuasive." K.O. v. Sec'y of Health & Hum. Servs., No. 13-472V, 2016 WL 7634491, at *12 (Fed. Cl. Spec. Mstr. July 7, 2016) (internal citations omitted) (first quoting Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 743 (2009); and then quoting Althen, 418 F.3d at 1280).

Here, Dr. Gershwin did not offer any persuasive reasons for extrapolating from the flu vaccine to the Tdap vaccine. See K.O., 2016 WL 7634491, at *12 (finding the case reports offered by Petitioner as having even less value than case reports do generally because they reported a sequence in which a vaccine, but not the vaccine at issue, preceded the onset of the injury at issue (citing Campbell v. Sec'y of Health & Hum. Servs., 97 Fed. Cl. 650, 668 (2011))); Crosby v. Sec'y of Health & Hum. Servs., No. 18-1478V, 2021 WL 3464125, at *9 (Fed. Cl. Spec. Mstr. July 22, 2021) (declining to give substantial weight to an article because it was on a different vaccine than the one at issue making reasoning difficult); see also Deshler v. Sec'y of Health & Hum. Servs., No. 16-1070V, 2020 WL 4593162, at *19-21 (Fed. Cl. Spec. Mstr. July 1, 2020) (declining to attribute case reports on the flu vaccine to pneumococcal vaccines); McDonald v. Sec'y of Health & Hum. Servs., No. 15-612V, 2023 WL 2387844, at *23 (Fed. Cl. Spec. Mstr. Mar. 7, 2023).

Finally, there are two other Program cases with reasoned analyses regarding a causation theory for GCA/PMR, and the special masters in those cases denied entitlement.[65] Suliman v. Sec'y of Health & Hum. Servs., No. 13-993V, 2018 WL 6803697 (Fed. Cl. Spec. Mstr. Nov. 27, 2018); Kelly v. Sec'y of Health & Hum. Servs., No. 17-1475V, 2022 WL 17819157 (Fed. Cl. Spec. Mstr. Oct. 12, 2022). While the mechanisms may differ, GCA/PMR has been rejected as a vaccine related injury due to insufficient evidence to support causation. Although decisions of other special masters are not binding, the undersigned generally agrees with the reasoning of her colleagues in these cases. See Boatmon, 941 F.3d at 1358; Hanlon v. Sec'y of Health & Hum. Servs., 40 Fed. Cl. 625, 630 (1998), aff'd, 191 F.3d 1344 (Fed. Cir. 1999).

In Suliman, the Petitioner alleged she suffered PMR and/or myositis as a result of the Tdap vaccine. Suliman, 2018 WL 6803697, at *25-27. Petitioner's expert offered the autoimmune syndrome induced by adjuvants ("ASIA") theory. Id. The special master determined Petitioner's expert did not effectively explain how the aluminum adjuvant in the Tdap vaccine could cause PMR and/or myositis. Id.

In Kelly, the Petitioner alleged she suffered PMR as a result of the flu vaccine. Kelly, 2022 WL 17819157, at *1. Petitioner's expert offered molecular mimicry as the theory of causation. Id. at *6. Specifically, Petitioner's expert proposed that hemagglutinin contained in the flu vaccine cross-reacted with collagen in the body. Id. The special master found that the medical literature filed and relied on by Petitioner did not identify hemagglutinin and collagen as structurally similar. Id. at *9; see also C.P. v. Sec'y of Health & Hum. Servs., No. 14-917V, 2019 WL 5483621, at *26, *28 (Fed. Cl. Spec. Mstr. Aug. 21, 2019) (denying entitlement where the theory was molecular mimicry and there was no evidence of homology).

Overall, the undersigned finds that here, Petitioner's theories are unsupported by medical or scientific facts, research, or any other reliable evidence. Moreover, the theories are speculative and/or conclusory in nature. When evaluating whether petitioners have carried their burden of proof, special masters consistently reject "conclusory expert statements that are not themselves backed up with reliable scientific support." Kreizenbeck v. Sec'y of Health & Hum. Servs., No. 08-209V, 2018 WL 3679843, at *31 (Fed. Cl. Spec. Mstr. June 22, 2018), mot. for rev. denied, decision aff'd, 141 Fed. Cl. 138, aff'd, 945 F.3d 1362 (Fed. Cir. 2020). The undersigned will not rely on "opinion evidence that is connected to existing data only by the ipse dixit of the expert." Prokopeas v. Sec'y of Health & Hum. Servs., No. 04-1717V, 2019 WL 2509626, at *19 (Fed. Cl. Spec. Mstr. May 24, 2019) (quoting Moberly, 592 F.3d at 1315). Instead, special masters are expected to carefully scrutinize the reliability of each expert report submitted. See id.

In summary, Petitioner has failed to offer a sound and reliable medical theory in support of his claim. Thus, the undersigned finds Petitioner has failed to provide preponderant evidence with respect to the first Althen prong.

[65] In a third case, diagnosis was at issue and the special master found that preponderant evidence did not show that Petitioner had the injury alleged (PMR). Giesbrecht v. Sec'y of Health & Hum. Servs., No. 16-1338V, 2023 WL 2721578, at *5-7 (Fed. Cl. Spec. Mstr. Mar. 30, 2023).

B. Althen Prong Two

Under Althen Prong Two, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras, 993 F.2d at 1528. Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, Petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Since Petitioner failed to prove Althen Prong One, it follows that he cannot prove Althen Prong Two. However, even if Petitioner had proven Althen Prong One, the undersigned finds Petitioner has failed to show by preponderant evidence that there is a logical sequence of cause and effect showing Petitioner's Tdap vaccine caused his GCA/PMR.

Fundamental to Dr. Gershwin's opinion is that GCA occurs in a genetically predisposed individual. He filed medical literature supporting this notion. See Pet. Ex. 50 at 5 (suggesting that reports from cases in first degree relatives and twins support a genetic predisposition to GCA). And an association has been suggested between the HLA haplotype[66] and GCA.

In response, Dr. Wilfong raised concerns about attributing causation to a genetic mutation or abnormality, when it is not known, particularly given that it is the "linchpin" in terms of causation as described by Dr. Gershwin. See Tr. 105. While an HLA haplotype has been suggested, a genetic mutation involved in disease pathogenesis has not been specifically identified. Moreover, whether Petitioner has the relevant genetic predisposition is also not known as it does not appear that Petitioner had HLA testing, or any other genetic tests to determine whether he had any predisposition to GCA. As such, this fundamental aspect of Dr. Gershwin's opinion is without any factual foundation and is therefore speculative.

[66] The specific haplotype associated with GCA is HLA-DRB1 *04 and the "risk of ocular involvement" has been reported. Pet. Ex. 50 at 5. For additional haplotypes found in GCA patients, see Pet. Ex. 50 at 5 tbl.1.

When evaluating whether petitioners have carried their burden of proof, special masters consistently reject "conclusory expert statements that are not themselves backed up with reliable scientific support." Kreizenbeck, 2018 WL 3679843, at *31.

Secondly, Dr. Gershwin further explains that in addition to genetic susceptibility, there is senescence, or aging of the endothelial cells and vessels. Tr. 36. He posits that the antigenic trigger occurs due to the senescence or "the aging endothelial cells and aging vessels." Tr. 36. He explains that the "presentation of GCA consists[] of a broad spectrum of clinical laboratory abnormalities that are attributable to ischemia . . . and systemic inflammation." Pet. Ex. 23 at 6; Tr. 28. It is not known why only certain arteries are affected by GCA, but the reasons may include genetic phenotypes as well as the "senescent component of endothelial cells." Tr. 29.

Petitioner underwent a left temporal artery biopsy on October 11, 2016, which revealed "features consistent with vasculitis, including [GCA]." Pet. Ex. 3 at 319; see also Pet. Ex. 3 at 173 (Dr. Li determining the MRI and biopsy studies were "suggestive of large vessel vasculitis"). But there is no evidence here that Petitioner specifically had aging of his endothelial cells or blood vessels. Because there is no evidence that Petitioner has a genetic susceptibility or senescence, it is speculative as to whether Petitioner meets the fundamental requirements for disease development according to Dr. Gershwin's theory. Although it is not clear that testing could have been performed to determine whether Petitioner had a genetic abnormality or senescence of his blood vessels, the lack of factual evidence is nevertheless problematic.

Next, the undersigned finds that while some of Petitioner's treating physicians documented his reports of symptoms and/or their temporal association with vaccination, they did not opine that his Tdap vaccine caused his illness.

Treating physician statements are typically "favored" as treating physicians "are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" Capizzano, 440 F.3d at 1326 (quoting Althen, 418 F.3d at 1280). However, no treating physician's views bind the special master, per se; rather, their views are carefully considered and evaluated. § 13(b)(1); Snyder, 88 Fed. Cl. at 746 n.67. "As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Welch v. Sec'y of Health & Hum. Servs., No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019).

Several of Petitioner's treating physicians and health care providers noted that Petitioner associated his symptoms to either his Tdap vaccine or a long bike ride. At a physical therapy visit, "reaction to booster shot" was documented. Pet. Ex. 8 at 10. But that entry was not made by a physician and appears to be a recitation of what Petitioner told the physical therapist.

Rheumatologist Dr. Kiehn's initial assessment was "inflammatory arthritis," and she questioned whether it was due to Tdap (reactive) or an onset of inflammatory arthritis. Pet. Ex. 1 at 10. She informed Petitioner that "time [would] help differentiate" the two proposed causes.

Id. In later records, Dr. Kiehn's assessment was GCA and inflammatory arthritis. She did not attribute these diagnoses as reactive to the Tdap vaccination. See Pet. Ex. 121 at 4.

When Petitioner was admitted to the hospital for a work-up, he was seen by Dr. Wehbe. Although Dr. Wehbe noted in the history that Petitioner received a Tdap vaccination, he did not opine that the vaccination played a causal role in the suspected vasculitis or GCA/PMR. Pet. Ex. 3 at 161. Petitioner was also seen during that same hospitalization by neurologist Dr. Katznelson. An allergy to the Tdap vaccine was noted, but without explanation. Dr. Katznelson also questioned whether Petitioner had some "hypersensitivity reaction" to the vaccination, but characterized this as only a "possibility." Pet. Ex. 3 at 116. Opinions expressed as possibilities, however, are not sufficient to establish causation. See, e.g., Waterman, 123 Fed. Cl. at 573-74; Moberly, 592 F.3d at 1322. In subsequent records, Dr. Katznelson did not reference Petitioner's condition as a hypersensitivity reaction, and he did not document any opinion causally associating Petitioner's GCA/PMR to his vaccination.

Other specialists, including Dr. Li, Dr. Blair, and Dr. Thompson did not document any association between Petitioner's symptoms and his vaccination.

After reviewing the medical records, while some doctors noted a potential association between vaccination and onset, the undersigned finds that none of Petitioner's treating physicians opined that his Tdap vaccination caused his GCA/PMR. "A treating physician's recognition of a temporal relationship does not advance the analysis of causation." Isaac v. Sec'y of Health & Hum. Servs., No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012); see also A.T. v. Sec'y of Health & Hum. Servs., No. 16-393V, 2021 WL 6495241, at *28 (Fed. Cl. Spec. Mstr. Dec. 17, 2021) (finding that Petitioner's treating physicians "considered, though did not conclude," that Petitioner's vaccine significantly aggravated her condition); Robertson v. Sec'y of Health & Hum. Servs., No. 18-554V, 2022 WL 17484980, at *17 (Fed. Cl. Spec. Mstr. Dec. 7, 2022) (finding treating physicians' statements of mere suspicion fall short of an opinion supporting vaccine causation); Cedillo v. Sec'y of Health & Hum. Servs., 617 F.3d 1328, 1347 (Fed. Cir. 2010) (concluding the special master did not err in affording little weight to the opinions of Petitioner's treating physicians where "none of the treating physicians concluded that the [] vaccine caused [Petitioner's] [condition]").

Accordingly, the undersigned finds that Petitioner failed to satisfy his burden under Althen Prong Two.

C. Althen Prong Three

Althen Prong Three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." Id. The Petitioner must offer "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773

F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542; see also Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer, 100 Fed. Cl. at 356 (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that [P]etitioner must posit a medical theory causally connecting the vaccine and injury").

The parties stipulated, and the experts agree, that Petitioner received a Tdap vaccine on August 4, 2016, and approximately 19 days later, he developed GCA and PMR. Joint Prehearing Submission at 1.

Respondent does not contest that there is a temporal association between Petitioner's Tdap vaccination and the onset of his GCA/PMR. See Resp. Ex. B at 7 (Dr. Wilfong agreeing "there is a temporal correlation between the Tdap vaccine and the onset of [Petitioner's] [] symptoms"); see also Tr. 90 (same). Thus, Petitioner has provided preponderant evidence satisfying Althen Prong Three. However, a temporal association, without more, is insufficient. Moberly, 592 F.3d at 1323; Grant v. Sec'y of Health & Hum. Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("[A] proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury."). Thus, Petitioner is not entitled to compensation.

VI. CONCLUSION

The undersigned extends her sympathy to Petitioner for the pain and suffering that he experienced due to his illness. The undersigned's Decision, however, cannot be decided based upon sympathy, but rather on the evidence and law.

For the reasons discussed above, the undersigned finds that Petitioner has failed to establish by preponderant evidence that his Tdap vaccine caused his GCA and/or PMR. Therefore, Petitioner is not entitled to compensation and the petition must be dismissed. In the absence of a timely filed motion for review pursuant to Vaccine Rule 23, the Clerk of Court **SHALL ENTER JUDGMENT** in accordance with this Decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master